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EXPERIMENTAL EVIDENCE THAT LESIONS WITH THE BASIC CHARACTERISTICS OF RHEUMATIC CARDITIS CAN RESULT FROM ANAPHYLACTIC HYPERSENSITIVITY

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The view that the lesions of rheumatic fever may be due not to a direct action of a bacterial toxin or an invisible virus, but may represent the effects of a hypersensitive reaction to bacterial products has been suggested repeatedly. Swift (1), Coburn (2) and others have been active proponents of this view in the United States; and in other countries, particularly in Germany, the possibility that the lesions are a manifestation of hypersensitivity has long been widely discussed. The apparent specificity of the lesions has, however, been insistently advanced as an argument against the rôle of hypersensitivity, for the Aschoff body and the valvular lesions do not resemble the usual inflammatory-necrotic lesions of "bacterial type" hypersensitivity produced by bacterial proteins (e.g., tuberculoprotein) in the body sensitized by infection. A number of investigators have attempted to produce Aschoff bodies by injecting bacteria into sensitized animals. The illustrations of the lesions so produced do not permit one to accept them as Aschoff bodies. Gross and his co-workers (3) have carefully and critically repeated much of this work with quite negative results. Some years ago Klinge (4), and Vaubel (5) and Junghans (27), his associates, reported that they had produced lesions resembling those of rheumatic carditis by repeated injections of horse serum into rabbits. Here, again, the illustrations of the lesions are quite inadequate to carry conviction. Bruun (45) repeated their experiments and, though he observed cardiac lesions in his animals, he concluded: "In my experiments it has *not* been possible to produce an analogon to Aschoff's nodule" (Bruun's italics). However, he believed that the lesions that he observed were sufficiently suggestive to regard it as probable that rheumatic lesions develop on a hypersensitive basic. The illustrations in all of the papers dealing with

the experimental production of rheumatic lesions have failed to convince most readers that the lesions bear any basic resemblance to those of rheumatic carditis. The general attitude is typified by that in the excellent paper of Gross and his associates (3) who state that the published illustrations in the papers dealing with the experimental production of lesions of the Aschoff body type are "entirely unconvincing."

In recent studies (6) (7) (8) we were able to show that generalized vascular lesions identical with those of periarteritis nodosa can result from hypersensitivity reactions of the serum sickness (anaphylactic) type. During these studies we observed in the hearts of some of the experimental animals lesions which, in their basic characteristics, bore so striking a resemblance to those of rheumatic carditis that we have carried out a further investigation of the matter. The results of these studies have impressed us so strongly with the similarity between the basic character of the cardiac tissue reaction of rheumatic fever and that of the animals with induced serum sickness that we regard it as desirable to place the observations on record. It is our belief that while most of the experimentally produced "rheumatic lesions" have been clearly quite different from those of the disease itself, some of the investigators, such as Klinge and his associates and Bruun, who have studied the tissues of *anaphylactically* sensitized animals subjected to contact with the specific antigen, and have reported the occurrence of lesions closely resembling those of rheumatic carditis, probably had before them lesions more suggestive than their illustrations indicate. Or it may be that the experimental method that we have used (the production of serum sickness) may be more suitable for the elicitation of the lesions than is the previously used procedure of repeated injections of smaller amounts of serum into sensitized animals.

We wish to emphasize at the outset that we are making no claim that the present observations settle with finality the question of the pathogenesis of the lesions of rheumatic fever, or that we have reproduced the disease picture as it so commonly occurs in man. In no instance has the cardiac tissue of our animals been peppered with typical Aschoff bodies, as is so often the case in rheumatic fever, permitting a diagnosis at a glance; and our studies of the joints are as yet incomplete. However, there have occurred valvular and myocardial lesions

which, in their situation and basic characteristics, conform so closely with those of rheumatic carditis that we believe that they may provide a fair measure of support for the view that the specific rheumatic lesions may themselves be manifestations of an anaphylactic hypersensitive reaction. Our purpose in this paper is to illustrate these lesions as clearly as possible, so that the reader may be provided with adequate means of forming his own opinion about the matter. In the present state of uncertainty regarding the pathogenesis of this important disabling disease, any pertinent evidence seems worthy of presentation.

The experimental procedure in this study has consisted in the sensitization of rabbits to sterile horse serum, without preservative,[1] under conditions that produce serum sickness (fever, erythema and sometimes oedema). This end can be attained in the rabbit, as in the human being, either by the intravenous injection of a single large amount of serum or by a second injection following an initial sensitizing one. The details of the procedure and the manifestations of the serum sickness have been described in our previous paper dealing with periarteritis nodosa (8), and need not be repeated here. The animals were killed at periods between one and 5 weeks following the systemic reaction. Not all of the rabbits so treated developed cardiac lesions of the specific rheumatic type. They were present in the sections of 11 out of 36 rabbits subjected to the serum injections (Nos. 13, 14, 47, 48, 52, 53, 58, 59, 62, 64, 65). It should be stated that adequate sections of the valve regions were lacking in 14 animals that were killed for study before our attention was attracted to this problem.

As is well known, the characteristic cardiac lesions of rheumatic fever consist in (1) focal alterations in the collagen of the connective tissue; (2) the presence of the Aschoff body; (3) focal and diffuse inflammatory lesions; (4) focal alterations in the cardiac muscle; and (5) verrucose valvular vegetations.

The *focal collagen alterations* characteristic of rheumatic fever consist in a separation of the fibers by oedema, swelling of the individual fibers, and finally degeneration of the fibers. In our experimental animals all of these alterations have occurred focally in the cardiac

[1] The serum was kindly supplied by the Medical-Research Division of Sharp and Dohme, Inc.

connective tissue. They have been most prominent in the valves and in the mural endocardium at and near the valvular attachment (Figs. 2, 3, 7, 8, 11).

The *Aschoff body* consists in a nodular collection of mononuclear cells that are usually grouped about, and sometimes dispersed in, a focus of damaged collagen. Not infrequently the cells are arranged in a palisade fashion at the margin of the focus of swollen, degenerated collagen fibrils. While lymphocytes, plasma cells and macrophages are not infrequently present in these lesions, the characteristic cells are large, with abundant cytoplasm which is often, but not always, basophilic, and with a nucleus which may be round, oval or, when large, irregular in outline. Frequently several nuclei are present. The nuclei are often rather clear, with chromatin condensed in the center and radiating in fine lines toward the nuclear membrane. In this they resemble the so-called "Anitschkow myocyte" (26), though the nuclei of the latter cells are usually more elongated. Typical "Anitschkow myocytes" are also present (Fig. 13). They may be found in or adjacent to the Aschoff bodies, and elsewhere in the damaged myocardial and endocardial connective tissue. The origin of these cells, and of the other large cells of the Aschoff body, is at present undecided. The Aschoff bodies are found most commonly adjacent to the blood vessels in the connective tissue septa of the myocardium, and in the mural endocardium particularly near the attachment of the valves. They also occur in the pericardium, and in the substance of the valve leaflets.

In the hearts of our animals focal accumulations of cells, in some instances closely resembling the Aschoff body, are present. In these cellular collections there are, aside from the ordinary mononuclear inflammatory cells, large cells, often basophilic and quite like those that characterize the Aschoff body. Some have large, single nuclei, round, oval or bizarre-shaped (Figs. 2, 3, 7); others are multinuclear (Figs. 2, 12); and cells of the "Anitschkow myocyte" type are plentiful (Figs. 12, 14, 15). In numerous instances the cells are grouped about a focus of swollen and degenerated collagen fibrils, sometimes forming a rather palisade-like border closely resembling that familiar in rheumatic lesions. This is particularly evident in the valve leaflets near their base and in the endocardium near the valvular attach-

ments (Figs. 2, 3, 7, 8, 11). While perivascular cellular accumulations are plentiful in the myocardium, foci resembling Aschoff bodies are infrequent there. Figures 1, 4, 5, 6 and 15 illustrate perivascular myocardial lesions suggestively like Aschoff bodies. The relation of these cellular accumulations to degenerated collagen is, however, less striking than in the valvular and endocardial lesions. It should be stated that the lesions resembling Aschoff bodies are not present in the hearts of these animals in a profusion that causes them to spring to the eye in a casual, low-power survey of the sections. A more careful study of the tissues, particularly in the favored situations mentioned above, is required for their discovery. Cases of rheumatic carditis in which search is required for the discovery of single Aschoff bodies are, of course, familiar. The higher magnifications are of great assistance in the study of the character of the lesions in the diminutive heart of the rabbit.

Non-specific inflammatory lesions are common in the heart in rheumatic fever. These lesions, which occur in the connective tissue of the myocardium, endocardium, pericardium and valves consist ordinarily in oedema with mononuclear cell infiltration (lymphocytes, plasma cells, macrophages), though in acute lesions polymorphonuclears are also present. These inflammatory infiltrations are most prominent in the pericardium, the base of the valve leaflets, and in the mural endocardium at the insertion of the valves (Fig. 16). In our animals precisely similar inflammatory infiltrations were present and, as in rheumatic fever, they were especially prominent in the pericardium (Fig. 24), the base of the valves (Fig. 22, 23), and the mural endocardium at the valvular insertions (Fig. 18).

Aside from occasional Aschoff bodies in the valves, the rheumatic *valvular lesions* consist in oedema, swelling and degeneration of collagen fibers, and inflammatory infiltrations that are predominantly mononuclear. Later, minute verrucose vegetations that are eosinophilic and structureless may appear over inflamed portions of the valves, particularly along the line of closure. Swift (9) has described very early cases providing evidence that inflammatory lesions and Aschoff bodies in the valves precede the appearance of the surface vegetations. In some of our animals, lesions in the valve substance of essentially the same character as those in fresh rheumatic carditis were prominent

(Figs. 2, 7, 8, 9, 10, 11, 12, 22). In some instances the cellular infiltrations produced projecting "vegetations" on the valves (Figs. 10 and 22). Although the valvular endothelium on the surface of these infiltrations was clearly damaged (the endothelial cells are swollen and often hyperplastic) we have so far found no eosinophilic "thrombus material" upon them.

In rheumatic fever *necrosis of small foci of cardiac muscle* occurs. This we have observed in only 4 of our animals. It is likewise slight or absent in many of the less severe instances of rheumatic carditis, even when Aschoff bodies are present.

Of course, in later stages the lesions of rheumatic fever undergo reparative fibrosis (Fig. 17). There is little doubt that many of the fresh lesions in our animals would also have become replaced by scar tissue with the passing of time. Indeed, in some of them vascularization and fibrosis were already under way (Figs. 18, 19, 20, 21). We are at present studying the effects of repeated hypersensitive reactions of the serum sickness type over a longer period of time.

DISCUSSION

In the present experiments focal lesions that in many important respects are strikingly similar to those characteristic of rheumatic carditis have occurred in the myocardial connective tissue, the mural endocardium and the valves of animals subjected to systemic hypersensitive reactions of the serum sickness (anaphylactic) type. A careful study of these lesions shows that their nature and situation correspond in fundamental ways to those of the peculiar tissue reaction characteristic of rheumatic carditis; *viz.*, focal oedema of the connective tissue with swelling and degeneration of the collagen fibrils; inflammatory pericardial, valvular and mural endocardial infiltrations, the latter localized particularly at and near the insertions of the valves; and focal nodular accumulations of cells situated in the endocardium, in the valves, and adjacent to the arteries in the connective tissue septa of the myocardium. These cell accumulations in the experimental animals contain, in addition to macrophages and a few lymphocytes, the peculiar types of cells familiar in the Aschoff body and, as in the Aschoff body, the cells may be found collected about the periphery of a focus of degenerated collagen. This is particularly evident in the

substance of the valves and in the mural endocardium near the valvular attachments.

It is important to point out that the focal perivascular, valvular and endocardial accumulations of cells in our animals are very different from the inflammatory foci that are encountered in the hearts of some "normal" rabbits. We have examined the hearts of many control rabbits and have never seen a reaction of this type. Reference to the descriptions and illustrations in the paper of Miller (10), who made an especial study of the spontaneous interstitial myocarditis of rabbits, will show clearly that those lesions are quite different in nature and distribution from the lesions that form the subject of the present paper. Miller states specifically that the cells in the spontaneous myocarditis "exhibit an outspoken dissimilarity to the type cells of an Aschoff body," and furthermore, that "no lesion was ever found in the valves or at the bases of the valves." We have pointed out above that cells morphologically identical with the type cells of the Aschoff body are present in our focal experimental lesions, and that the valves and their bases are the sites most commonly involved.

It should be stressed that the lesions in our experimental animals developed as a result of hypersensitivity of the *anaphylactic* type. In most considerations of the relation of hypersensitivity to rheumatic lesions the discussion is concerned with hypersensitivity of the "tuberculin type", which differs in a number of important respects from the anaphylactic type (11). Concentration upon the tuberculin type of hypersensitivity in relation to rheumatic fever has doubtless been the result of the natural attempt to link the lesions with streptococcal infection, for it is the tuberculin type of hypersensitivity that is ordinarily considered in relation to infection. Infection with bacteria, fungi and filterable viruses gives rise to the tuberculin type of hypersensitivity, manifested in skin tests by a delayed and prolonged inflammatory reaction to the injection of the specific protein of the microörganism, as contrasted with the prompt and evanescent wheal and erythema of an anaphylactic local reaction. It is important to remember, however, that anaphylactic hypersensitivity to bacterial constituents may also develop during infection. Pneumococcal infection, for example, may give rise to both the anaphylactic and the tuberculin type of hypersensitivity. It is the capsular carbohydrate

of the pneumococcus that is responsible for the anaphylactic type of hypersensitivity, and the somatic protein that is responsible for the tuberculin type (12). The same is true of the tubercle bacillus. The protein is responsible for the development of the tuberculin type of hypersensitivity, but the infected body may become anaphylactic to the carbohydrate of the bacillus (13). The development of anaphylactic hypersensitivity to the bacterial carbohydrate has also been demonstrated in the case of the Friedlander bacillus (14). In regard to the haemolytic streptococcus it is of interest that Coburn (2), in his study of the cutaneous hypersensitivity of rheumatic patients stated that "the immediate wheal and erythema type of reaction occurred frequently", but that these reactions "were not recorded." In that study Coburn used a nucleoprotein fraction of the streptococcus as the test material, and his observations were confined to the tuberculin type of hypersensitivity. In view of the results of the present experiments it will be of interest to study pointedly the anaphylactic reactivity of rheumatic patients, not only to the protein of the streptococcus but also to the streptococcal carbohydrate.

A consideration of the matter brings one to realize that there are a number of pertinent circumstances that are at least consistent with the view that the lesions of rheumatic fever may be results of the *anaphylactic* type of hypersensitivity. In the first place, all students of the pathology of rheumatic lesions are agreed that a fundamentally important manifestation of the condition is focal injury to the connective tissue, characterized by oedema, with swelling and degeneration of the collagen fibrils. It has long been recognized by students of local anaphylactic reactions that precisely these alterations are the primary and characteristic effects of the anaphylactic reaction upon the connective tissue (15) (16).

In the second place, it is well known that during the acute attacks of rheumatic fever there often occur inflammatory-necrotic arterial lesions (the so-called "rheumatic arteritis") which may closely resemble the vascular alterations of periarteritis nodosa. This was pointed out by Aschoff (25) in his original paper on rheumatic carditis, by Geipel (32) shortly after, and has been confirmed repeatedly (33). It is true, as Von Glahn and Pappenheimer (29) point out, that thrombosis and aneurysm formation in the affected vessels is uncommon in rheumatic arteritis, but there are innumerable affected vessels

in non-rheumatic periarteritis nodosa also, in which these accidents do not occur. The above writers, themselves (30), and others as well (31) have described thrombosis of affected rheumatic coronary arteries; and beginning aneurysm formation also has been described (32). The recent demonstration that periarteritis nodosa can result from anaphylactic hypersensitivity (8) may therefore serve as supporting evidence for the view that the rheumatic lesions may likewise be results of this type of hypersensitivity. Rheumatic carditis, of course, may occur in the absence of periarteritis nodosa-like vascular lesions, and periarteritis nodosa is ordinarily unaccompanied by carditis of the characteristic rheumatic type. However, focal or diffuse carditis does sometimes occur in association with periarteritis nodosa in man (6). It is of interest that Lamb (34), in a review of 40 cases of periarteritis nodosa, described the occurrence of erythematous or haemorrhagic skin erruptions, at times associated with urticaria, in 10 cases. Thirty-nine per cent of the 40 cases had joint pains, "often quite severe, usually involving more than one joint, and behaving very much like acute rheumatic fever."

In connection with the fact, mentioned in the preceding paragraph, that an anaphylactic reaction may produce periarteritis nodosa in some individuals and cardiac lesions of the rheumatic type in others, it may be worth recalling that there is a marked individual predisposition governing the site at which anaphylactic reactions will produce their effects when the sensitized body is exposed to the specific antigen. For example, five individuals may become sensitized to egg protein. Following the ingestion of eggs one may develop only urticaria; the second may react characteristically by developing an asthmatic attack; the third may regularly have an attack of abdominal pain and vomiting; the fourth may always have an attack of purpura; and the fifth may exhibit a combination of these effects. Just what factors govern this individual local tissue predisposition in the sensitized body is an unsolved problem at present, and one of great theoretical and practical interest. The existence of the fact, however, should be borne in mind in the consideration of the question why some sensitized individuals may develop lesions of the rheumatic type on exposure to the antigen, and others, similarly sensitized, may develop arterial lesions or other effects.

In the third place, it is of interest that, particularly in localities in

which the more fulminant forms of rheumatic fever are seen, skin lesions of the anaphylactic type and which are familiar in serum sickness (urticaria, erythemas) occur not infrequently during rheumatic attacks. Coburn (2) observed skin lesions of this type in 22.4 per cent of 162 carefully studied rheumatic patients. Holt and McIntosh (17), commenting on the occurrence of erythema marginatum, state that "unless this occurs as a manifestation of serum disease it is nearly always rheumatic in origin."

In the fourth place, purpura is a recognized manifestation of acute rheumatic fever. Coburn (2) noted the occurrence of purpura in 7 per cent of his series of rheumatic cases. Holt and McIntosh state that during rheumatic exacerbations "purpuric eruptions are not infrequent" (17). In parallel, purpura is a recognized manifestation of anaphylactic hypersensitivity. It occasionally occurs during serum sickness (18); Alexander and Eyermann (19) reported nine cases of hypersensitivity to foods, in which attacks of purpura could be produced by causing the patients to ingest the specific food-stuff; and some cases of "spontaneous" purpura are associated with anaphylactic skin eruptions (urticaria, erythemas) fever and arthritis. The difficulty of distinguishing the latter cases from acute rheumatic fever is recognized (17).

In the fifth place, tissue eosinophilia is a hall-mark of local anaphylactic reactions, and we should like to emphasize that tissue eosinophilia appears to be more frequent in acute rheumatic carditis than is ordinarily appreciated. The presence of eosinophils in rheumatic hearts has been described repeatedly (39) (40), and there have been several reports of extensive infiltration with eosinophils in rheumatic hearts containing Aschoff bodies (25) (28); yet many text-book descriptions of the rheumatic cardiac lesions still fail to mention the presence of these cells. In a study of 18 cases of acute rheumatic carditis from this standpoint we have found that a third of the cases contain focal areas in which high-power fields are peppered with these cells. The great majority of the black dots in the endocardial lesion in Figure 16, for example, are eosinophils. They are ordinarily infrequent or absent in the well-developed Aschoff body, but occur in lesions of the inflammatory type, especially in the pericardium, in the lower layers of the endocardium of the left auricle,

and in the ventricular endocardium particularly at the insertion of the mitral valve. In view of the considerable numbers of these cells that are present in some of the fresh inflammatory lesions of acute rheumatic carditis, it may be surprising that they have been so widely neglected. This is probably because they are to be found only in very active, acute cases including acute exacerbations in chronic cases, and they disintegrate and disappear from the tissues long before the Aschoff body and the mononuclear infiltrations do. In the 18 cases with fresh rheumatic lesions, many eosinophils were found in focal areas in 6 cases, a moderate number in 3 cases, a few in 5 cases and no appreciable number in four cases.

In the sixth place, acute rheumatic fever has many features in common with the anaphylactic reaction of serum sickness. In both there may be fever, arthritis, anaphylactic cutaneous lesions, and arterial lesions of the periarteritis nodosa type; and the present studies show that a type of carditis similar to that of rheumatic fever may occur in experimental serum sickness. Because of the great rarity of autopsies on cases of human serum sickness, and because there has been little pointed clinical study of the heart in patients with serum sickness, little is known of the frequency with which cardiac lesions occur in this condition. That serum sickness rarely, if ever, produces permanent cardiac functional damage is evident. It would hardly be expected that one attack of anaphylactic carditis similar to that in our experimental animals would permanently disable the heart. In most cases the scattered lesions would, in all probability, heal leaving little or no functional damage. In rheumatic fever, likewise, there are many cases in which one attack leaves no permanent cardiac functional damage. While, as stated above, there has been very little careful study of the heart in serum sickness, there are nevertheless scattered reports in the literature indicating that this anaphylactic reaction may entail both anatomic and functional cardiac damage. de Lavergne, Morel and Jochum (20) reported the occurrence of transitory Stokes-Adams syndrome during serum sickness. Weill-Hallé and Lévy (21) observed the development, during serum sickness, of cardiac arrythmia and "a muffled first sound comparable to that which one may observe during the course of acute articular rheumatism". Their observation led them to suggest that systematic

and careful cardiological studies in cases of serum sickness might bring to light a greater frequency of cardiac disturbances than is appreciated at present. Wadsworth and Brown (22) observed the development of cardiac functional abnormalities during serum sickness following prophylactic treatment with anti-tetanus serum. The alterations were compatible with those of rheumatic myocarditis, but the boy had had no previous history of tonsilitis, rheumatism, "growing pains" or heart trouble. Fox and Messeloff (38) reported a case of serum sickness, following anti-tetanus prophylaxis, in which transient electrocardiographic abnormalities were observed. Clark and Kaplan (24) have reported two cases of death following serum sickness in which, in addition to vascular lesions of the periarteritis nodosa type, interstitial myocarditis and valvulitis were found at autopsy. One case, autopsied three weeks after the appearance of serum sickness, showed periarterial foci of fragmented collagen associated with cellular accumulations. The authors state that "although some similarity exists between these vascular and perivascular alterations and those of rheumatic fever, no interstitial or perivascular structures were found which displayed close correspondence with the Aschoff nodule." It may be recalled that in rheumatic carditis, also, there are innumerable interstitial and valvular inflammatory infiltrations which are altogether non-specific. Furthermore, not all of our experimental animals with serum sickness developed lesions closely simulating Aschoff bodies.

In the seventh place, the focal character of the Aschoff body is not inconsistent with a reaction due to generalized anaphylactic hypersensitivity. Urticaria and periarteritis nodosa are both exquisitely focal lesions, and either or both can result from the entrance of the specific antigen into the circulation of the body with generalized anaphylactic hypersensitivity (6) (7) (8).

In the eighth place, it is of interest that Boots and Swift (37), from a careful study of the character of the synovial exudate aspirated from affected joints, concluded that "the synovial exudate (from the arthritis of serum sickness) is microscopically indistinguishable from that occurring in joints of patients with rheumatic fever."

In the ninth place, transient pareses are well known to occur during chorea associated with rheumatic fever (17), and there are also in

the literature many reports of transient pareses developing during serum sickness (44). While chorea, itself, is rare in serum sickness, occasional cases have been reported (43). It is of particular interest in the present connection that eosinophilia, often of considerable degree, frequently occurs during rheumatic chorea (17) (42).

Finally, in a consideration of the question whether rheumatic lesions may be manifestations of anaphylactic hypersensitivity, it is natural to inquire whether the anaphylactic arthralgia of serum sickness is relieved by salicylates, which are so efficacious in the relief

TABLE I

Clinical and Pathological Manifestations That Occur in Both Rheumatic Fever and Serum Sickness

	RHEUMATIC FEVER	HUMAN SERUM SICKNESS	EXPERIMENTAL SERUM SICKNESS
Fever	+	+	+
Arthritis	+	+	?
Urticaria	+	+	+**
Erythemas	+	+	+
Purpura	+	+	+*
Transient paresis	+	+	?
Myocarditis	+	+	+
Valvulitis	+	+	+
Pericarditis	+	?	+
Focal swelling and degeneration of collagen	+	+	+
Lesions of Aschoff body type	+	?	+
Tissue eosinophilia	+	+	+
Necrosis and inflammation of arteries	+	+	+

* Not observed in present experiments; described by Fleisher and Jones (41).

** See reference 44 for literature.

of the majority of cases of rheumatic arthralgia. While some writers state that salicylates are of little value in the arthralgia of serum sickness, the majority recommend their use. Kojis (23), in an extensive review of his personal observations on a large series of cases of serum sickness writes: "The arthritis was not relieved readily by salicylates in doses of 10 grains (0.65 gm.) by mouth, but great relief followed retention starch enemas containing 60 to 100 grains (4 to 6.5 gms.) of sodium salicylate."

We have been able to find very little documented evidence regarding

the effect of salicylates upon groups of patients with the arthraliga of serum sickness. Through the courtesy of Dr. Warfield T. Longcope we have studied 25 histories of patients who developed serum sickness with arthralgia on the medical wards of the Johns Hopkins Hospital. Thirteen of these cases were treated with salicylates (23387; 47318; 56416; 67043; 74013; 74765; 113355; 103258; 139887; 189135; 191250; 193746; 212518) and 12 were not (23610; 23741; 23911; 60878; 122282; 127987; 148019; 158047; 190373; 192042; 233072; 274196). Each series was composed of consecutively examined histories selected only from the standpoint of the requirement of adequate notes regarding the amount of salicylate, and an adequate recording of the joint symptoms.

Of the 12 cases untreated with salicylates, the arthralgia persisted for 4 to 7 days in 7 cases, for 3 days in one case, for 2 days in one case, and for 1 day in 3 cases.

In the treated group, salicylate therapy was begun on the day of onset of arthralgia in 10 cases. In 7 of these 10 cases the notes record relief of the joint pains within 24 hours; in three cases there was no appreciable effect of the drug upon the arthralgia. Of the remaining 3 treated cases, salicylate treatment was begun in two 1 day after the onset of arthralgia. Both of these cases were relieved within 24 hours after the first dose. In the remaining case salicylate treatment was begun 2 days after the onset of arthralgia, and the symptoms persisted for 7 days. The dosage of salicylate in the treated group varied between 2 and 6 gms. per day. It will be realized that these dosages are smaller than that commonly recommended for the relief of rheumatic arthralgia (35) (36).

The present experimental observations, together with the various considerations outlined above, are, at least, highly suggestive that the cardiac lesions of rheumatic fever may be the results of hypersensitive reactions of the anaphylactic type. While further work will obviously be required to place the pathogenesis of human rheumatic fever upon a secure foundation of knowledge, the present observations may serve to indicate desirable lines of study. As was stated at the beginning of this paper, our primary purpose has been to point out, with as clear illustrations as possible, the basic similarity of cardiac lesions of known anaphylactic origin to those characteristic of rheumatic carditis.

SUMMARY

Rabbits subjected to experimental serum sickness develop, in some cases, cardiac lesions that, in their basic characteristics, resemble closely those of rheumatic carditis. These lesions are illustrated, and circumstances compatible with the view that the lesions of rheumatic fever may be the results of focal reactions of the anaphylactic type are discussed.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Miss Dorothy Schmitt)

FIG. 1. Nodule of cells in connective tissue of myocardium adjacent to branch of coronary artery (rabbit 48).

FIG. 2. Multinuclear and mononuclear cells bordering focus of swollen, degenerated collagen fibrils in base of valve leaflet (rabbit 48).

FIG. 3. Swollen, degenerated collagen fibrils bordered by mononuclear cells, in mural endocardium at valvular attachment (rabbit 48).

FIG. 4. Focus of mononuclear cells in connective tissue of myocardium adjacent to branch of coronary artery (rabbit 58).

FIG. 5. Focus of mononuclear cells in connective tissue adjacent to partly degenerated wall of a coronary artery in myocardium (rabbit 13).

FIG. 6. Coronary artery in myocardium of rabbit 13. Endothelial lining outlined in ink, above which are erythrocytes. Focus of mononuclear cells grouped about oedematous collagen.

FIG. 7. Palisade of mononuclear cells bordering focus of swollen, degenerated collagen in valve (rabbit 48).

FIG. 8. Palisade of mononuclear cells at margin of focus of swollen, degenerated collagen in base of valve leaflet (rabbit 64).

FIG. 9. Accumulation of mononuclear cells extending along a valve leaflet of rabbit 15. The cells are like those in Fig. 12.

FIGS. 10, 11, 12. Nodular "vegetation" projecting from valve of rabbit 62. Fig. 10 low power. Fig. 11 shows swollen, degenerated collagen. Fig. 12 shows the types of cells. Note multinuclear cells. Two "Anitschkow myocytes" at left.

FIG. 13. "Anitschkow myocytes" in rheumatic lesion in human heart (Autopsy 13497). Note chromatin condensed into long central core with perpendicular chromatin projections extending toward nuclear membrane. Compare Figs. 12, 14 and 15.

FIG. 14. "Anitschkow myocytes" in lesion at base of valve in rabbit 59. Compare Fig. 13.

FIG. 15. "Anitschkow myocytes" in focus of mononuclear cells adjacent to coronary artery in myocardium of rabbit 13.

FIG. 16. Endocardial inflammatory lesion in a case of human rheumatic pancarditis with fresh Aschoff bodies (Autopsy 16401). The great majority of the inflammatory cells in this lesion are eosinophils. Compare Fig. 18.

FIG. 17. Organized, fibrous endocardial lesion in human rheumatic carditis (Autopsy 13519).

FIG. 18. Endocardial inflammatory lesion in rabbit 65. Vascularization is under way (arrows point to capillaries). Compare Fig. 16.

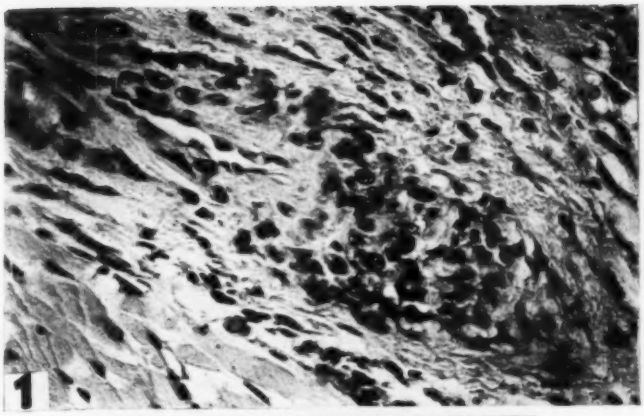
FIGS. 19 and 20. Organized endocardial inflammatory lesions in rabbit 59. Compare Fig. 17.

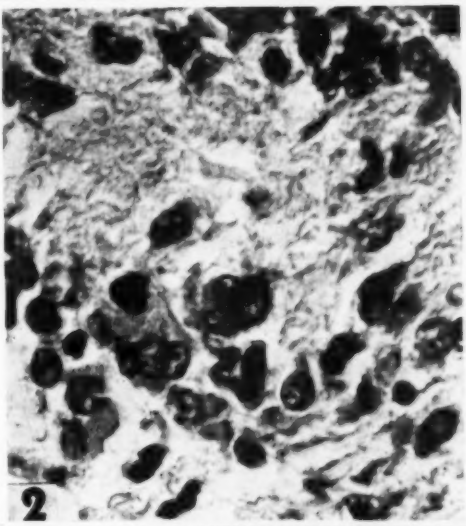
FIG. 21. Endocardial lesion in rabbit 52.

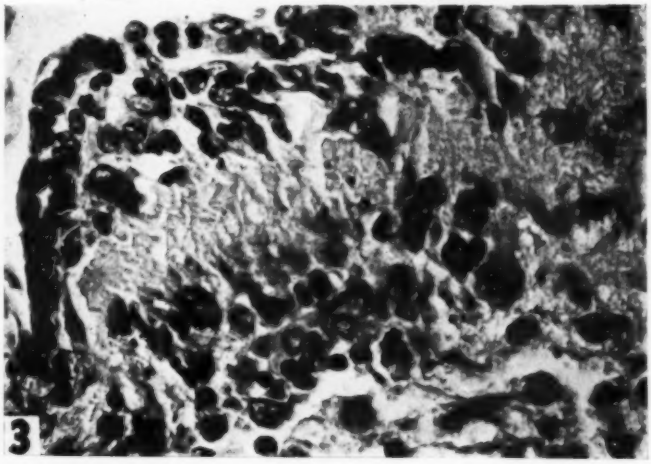
FIG. 22. Inflammatory lesion projecting from valve in rabbit 64.

FIG. 23. Subendocardial inflammatory lesion at base of valve in rabbit 64.

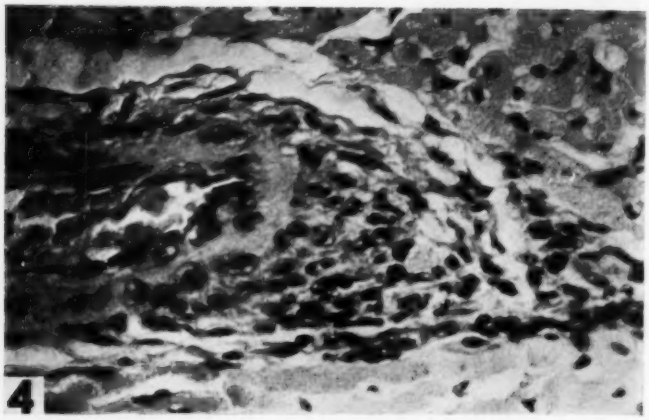
FIG. 24. Inflammatory lesion in visceral pericardium of rabbit 65.

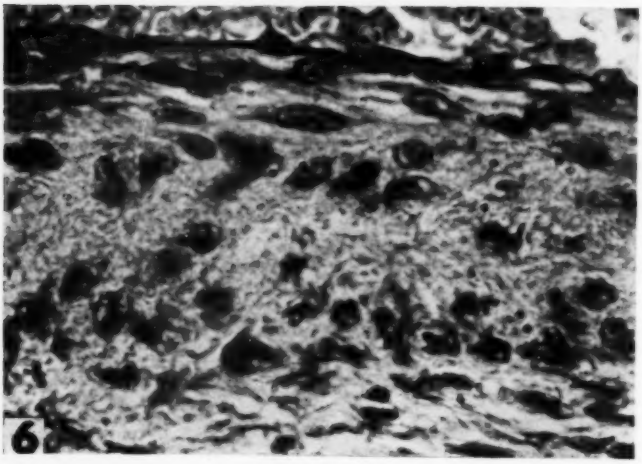




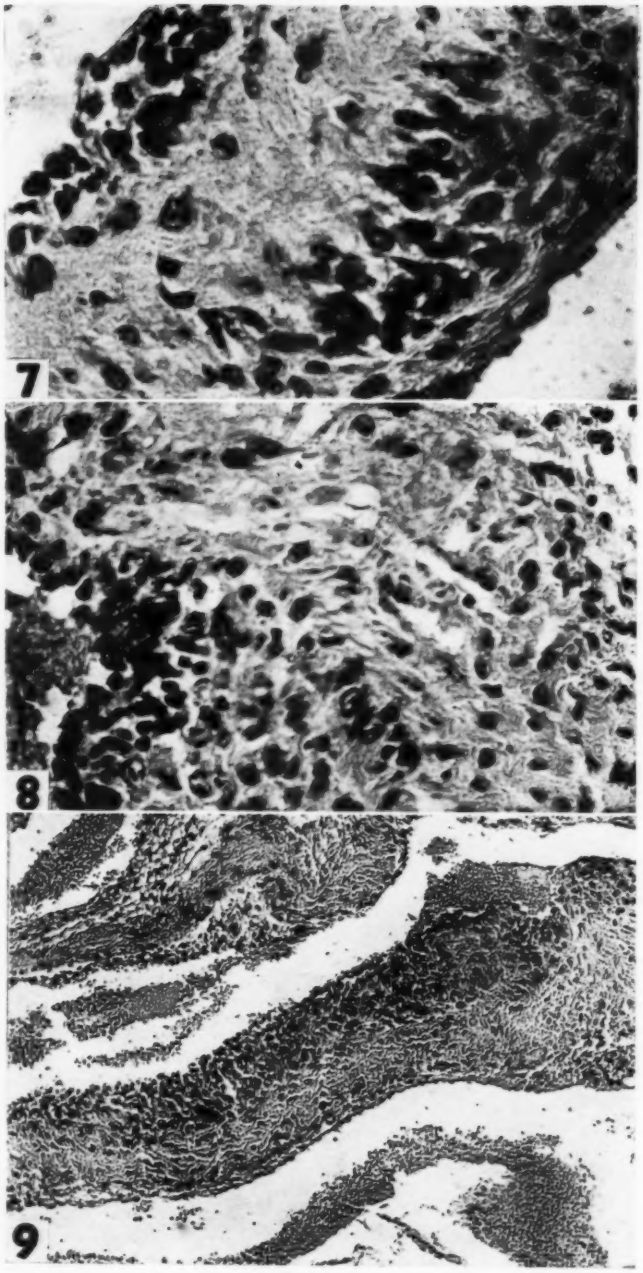


FIGS. 1–3

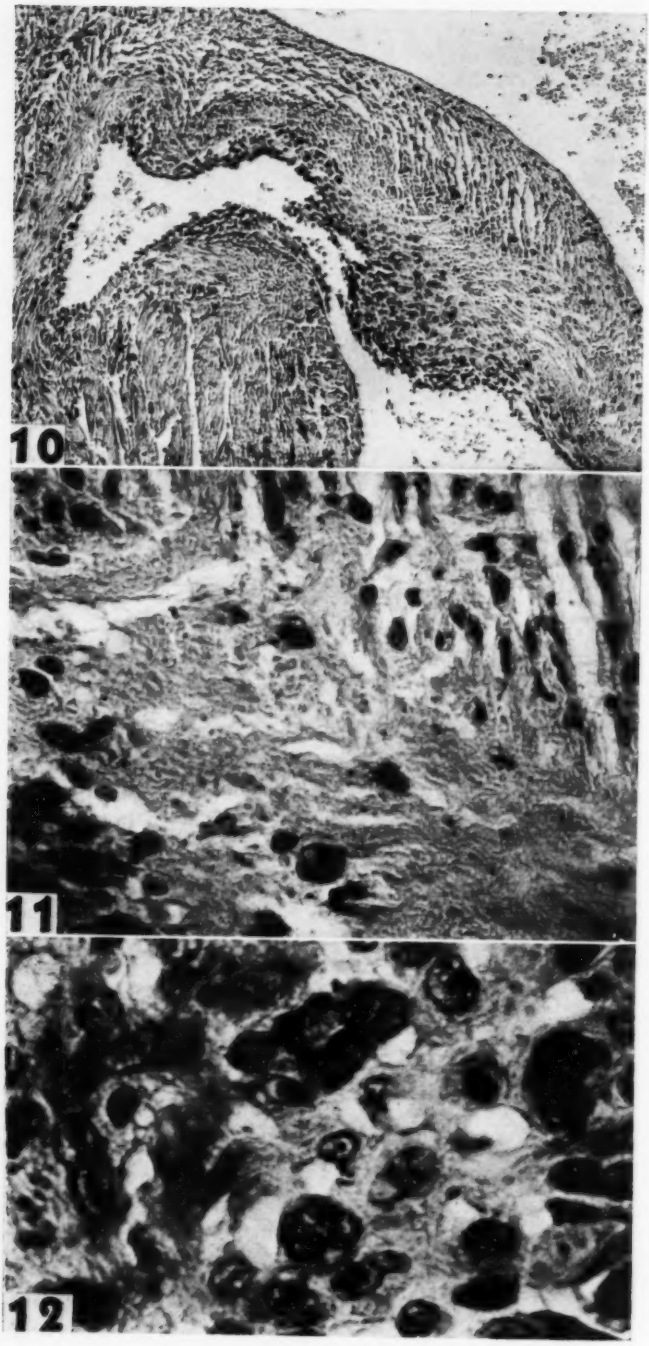




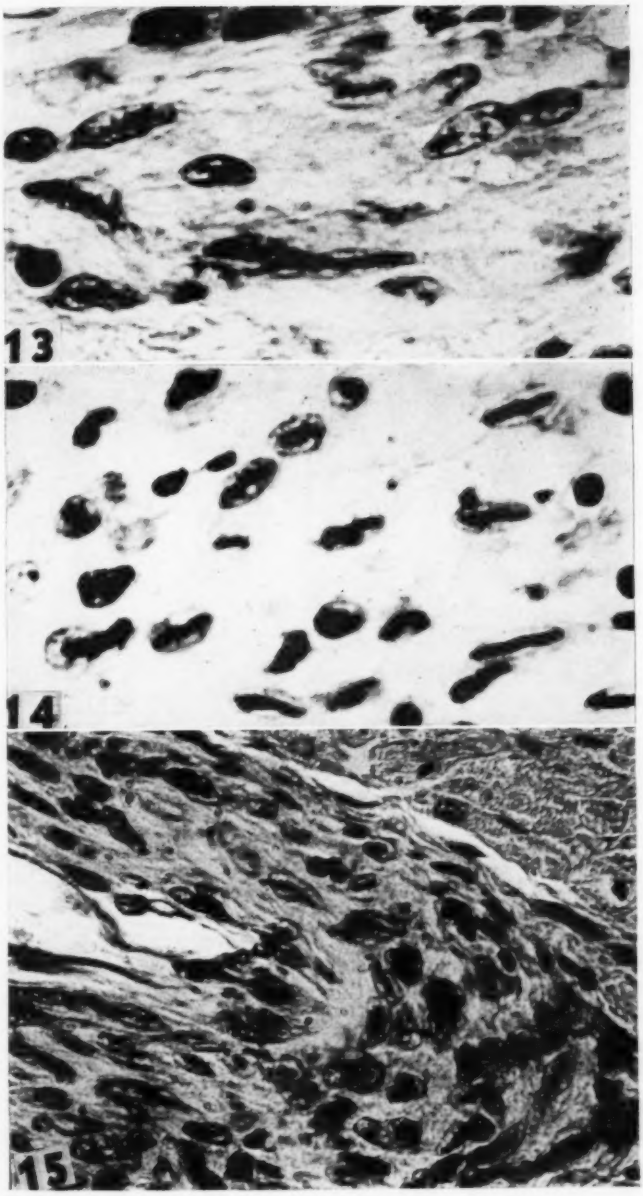
FIGS. 4–6



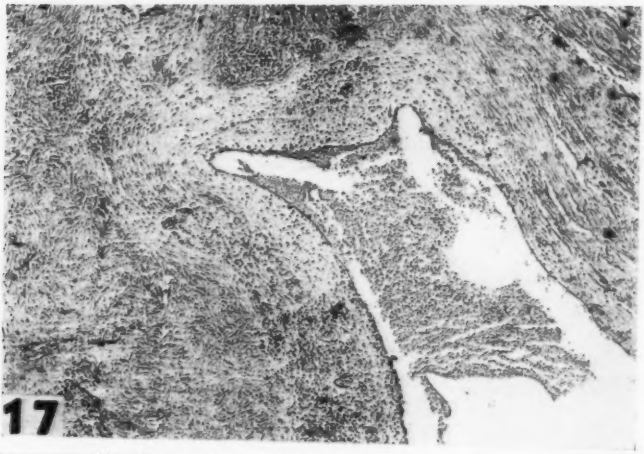
FIGS. 7–9

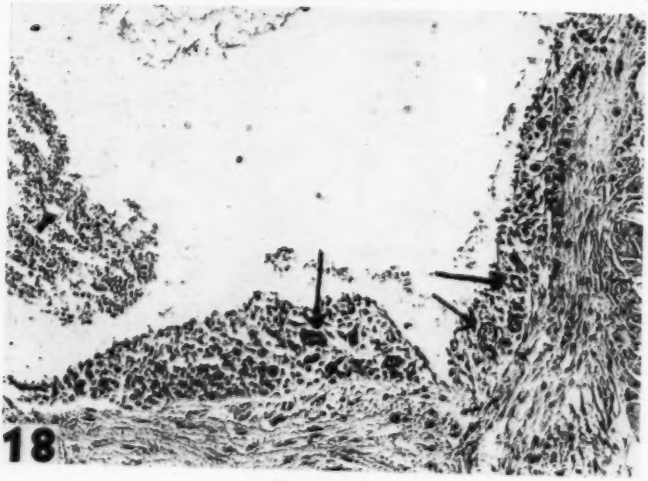


FIGS. 10–12

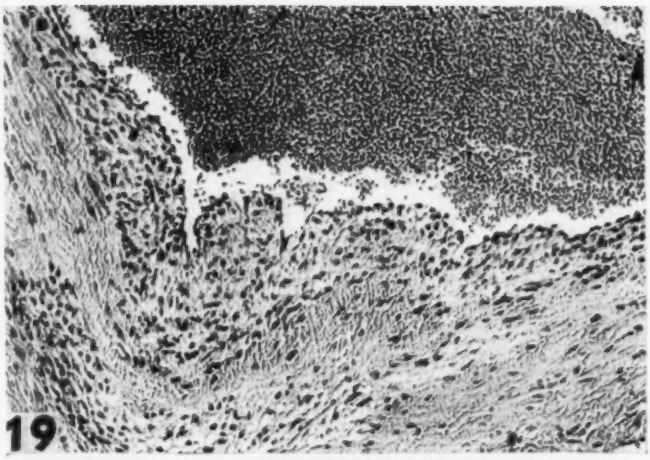


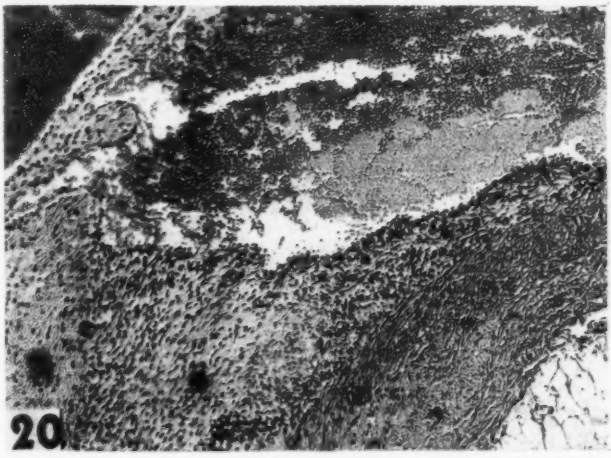
FIGS. 13–15

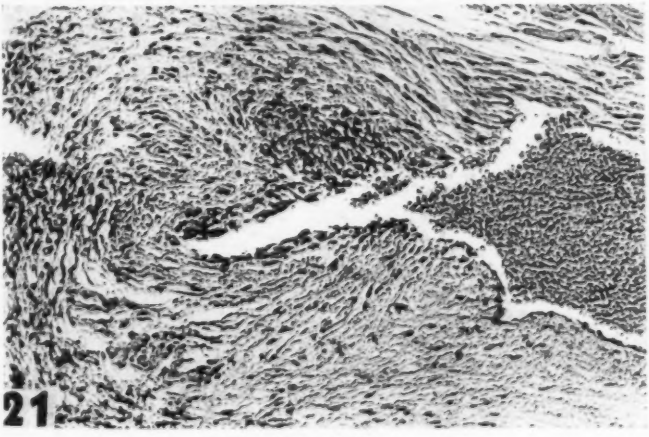




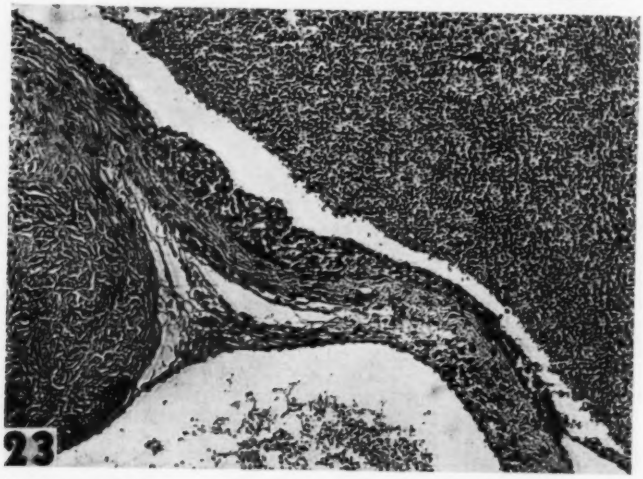
FIGS. 16–18

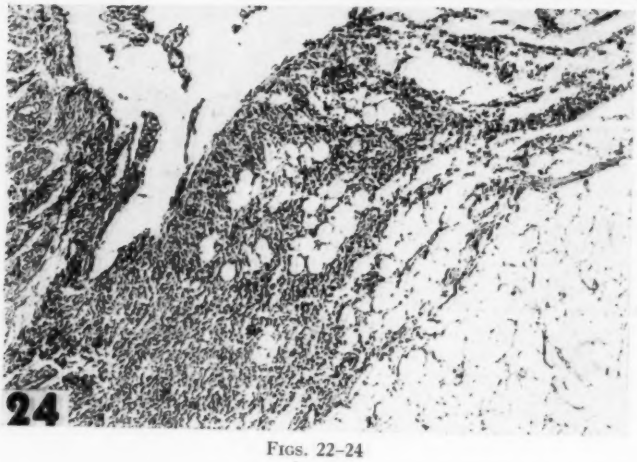






FIGS. 19–21





FIGS. 22–24

CEREBRAL MALARIA

A Case Report

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Because of the relative infrequency of the marked cerebral manifestations of malaria in the continental United States, and because of the more frequent occurrence of this clinical picture in many of the present war zones, it is considered worth while to present a detailed report of a case of cerebral malaria.

Malaria has a wide distribution over all parts of the tropical and subtropical world, and also over many temperate regions. *Plasmodium vivax* is the commonest etiologic agent in the temperate zones, and *Plasmodium falciparum* is encountered especially in badly infected districts in the warmer parts of the world. According to Stitt (1) the principal endemic area in the United States is in the Southeastern States. In the northern portion of this region, tertian malaria occurs almost entirely. However, south of the Chesapeake Bay much aestivo-autumnal malaria has been encountered. Here there must be cases of the cerebral type, but I am unable to find statistics concerning this. Faust (2) stated that the malarial mortality of 14 southern States, with an approximate population of 35 million, was 5.8 per 100,000 in 1938. Of these deaths, certainly a definite proportion must have been due to the cerebral form of the aestivo-autumnal infection.

From an epidemiologic view-point it is very interesting that malaria is highly prevalent in some islands of the South Pacific and absent in others. Whether this is due to certain habits of the anopheline mosquito, to chance, or to other unknown factors, is not clear. Thus, in Tahiti, Hawaii, Fiji, the Gilbert and Ellice Islands, Samoa, the Leeward Islands, the Marquesas and New Caledonia, there is no malaria. In the Solomons and New Hebrides there is a great deal of it.

It is interesting from a clinical viewpoint that *Plasmodium falciparum* almost exclusively produces pernicious attacks, and is the most

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dangerous type of malarial parasite. Stitt states that pernicious malaria may be of several types—cerebral, algid, and bilious remittent. In addition, pulmonary and cardiac forms have been described. In the cerebral form the parasites are found in great numbers in the capillaries of the brain. Why plasmodium falciparum should localize there much more commonly than the other malarial parasites is not clear. Bass thinks that the ovoid shape of the malignant tertian parasite renders it difficult for it to pass through capillaries which the flattened benign forms can traverse by infolding. Clinically, the predominant features of cerebral malaria may be hyperpyrexia, delirium, coma, convulsions, psychoses, and apoplectic phenomena.

I could find in the scanty available literature very little concerning renal changes in malaria. In the case to be reported there were urinary and blood pressure findings consistent with those that occur in acute glomerular nephritis. Because of the predeliction of *Plasmodium falciparum* to lodge in the capillaries of the brain and intestinal tract, it seems reasonable to assume that it may block the glomerular capillaries in a similar fashion.

S. B. (Number 1247, 18th General Hospital), a 25 year old white single male, entered the hospital January 22, 1943. The chief complaints were chills and fever.

P. H.: The patient was from Wildrose, North Dakota. He had always been quite healthy. He had had the usual childhood diseases. There had been no operations or injuries. He stopped school in the 8th grade at the age of 15 to work on his father's wheat farm. He continued to work on the farm until induction into the army April 25, 1941. His habits were good. He did not fail any grades in school, but stopped because his father needed him on the farm.

F. H.: Mother, father, one brother, and one sister, living and well. No tuberculosis, diabetes, or allergic diseases in the family. He left the United States on March 18, 1942 with his army unit. He arrived in Australia April 8, 1942, and after a few days there was sent to New Caledonia. He was in New Caledonia from April 19, 1942 to October 10, 1942. He was then transferred to Guadalcanal where he was stationed from October 13, 1942 to January 28, 1943. While in New Caledonia his health was excellent. At no time had he ever had any urinary symptoms. There is no malaria in New Caledonia.

P. I.: On December 16, 1942, the patient had a chill and developed generalized aching, headache and fever. He continued to have chills and fever every other night until he entered the hospital on Guadalcanal on December 23, 1942. He did not seek medical advice before this. On that day he had a chill and fever of 103°F., and on December 26 a chill with a fever of 102°F. On December 25 he had six or seven liquid stools, which did not contain blood. The diarrhea continued

for 2 days and then subsided. His recollection of malarial prophylaxis and treatment is not entirely clear. He thinks he was given quinine 0.6 gram daily, beginning October 10 and continuing 2 or 3 months. This was then discontinued, and he was given atabrine 48 mg. daily. While in the hospital on Guadalcanal, he knows he received quinine several times a day. Because of the above complaints he was evacuated from Guadalcanal to New Hebrides on December 28, 1942. His physical examination on January 2, 1943 in New Hebrides was reported as essentially negative, except for evidence of weight loss. The routine laboratory studies were negative except for a red blood cell count of 3,970,000 and a hemoglobin of 80 per cent. The white blood cell differential showed 54 per cent lymphocytes, and 18 per cent eosinophils. Treatment consisted of atabrine 0.1 gram, 3 times a day for 7 days, followed by a course of quinine hydrochloride, 0.6 gram 3 times a day for 7 days. He was also given ferrous sulphate and a vitamin complex. On January 3 his temperature was 99°F. and a malarial blood smear showed *Plasmodium falciparum* 4 plus (gametocytes only). On January 5 his icteric index was 3.3. On January 7 his weight was 173 lbs. (usual weight 200 lbs.) and his red blood cell count was 3,560,000. On January 9 a malarial blood smear was again positive for *Plasmodium falciparum* 4 plus (gametocytes only). A stool culture was negative. A note on January 11 stated that a repeated urinalysis was negative, and that he had had remittent fever from 99° to 102°F. for the past 3 days. He was started on quinine on that day. A note on January 13 stated that he had a daily fever of 100°F. On January 15, a malarial blood smear was positive for *Plasmodium falciparum* 4 plus (gametocytes only). On January 16, it was noted that there was slight pitting edema of the ankles. The red blood cell count was 2,050,000 with 45 per cent hemoglobin. There were 16 per cent eosinophils in the smear. On Jan. 17, a urinalysis was essentially normal. The N.P.N. was 33 mg. per cent. The edema was slightly increased. On January 18 he was given 500 cc. of citrated whole blood by the indirect method. On January 19 he was transferred to a hospital ship. It was stated that his condition was satisfactory. On January 19, a thick malarial blood smear was reported positive for *Plasmodium vivax*. On January 22, he was admitted to the 18th General Hospital.

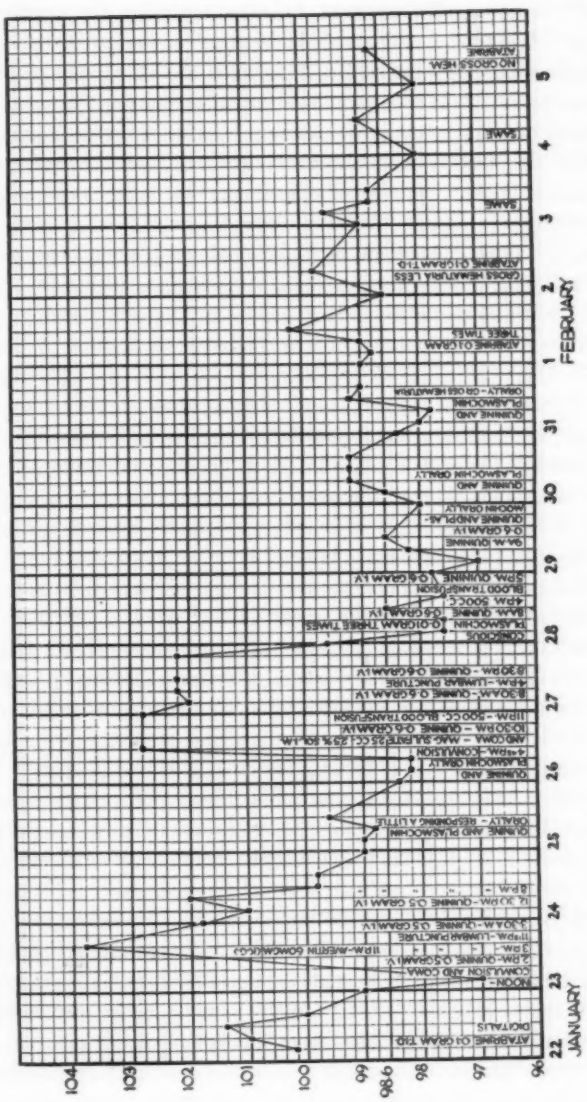
Examination on admission here showed temperature 100.4°F., pulse 80, blood pressure 170/110. The patient had evidently lost a great deal of weight. He was pale, and his skin was colored yellow from atabrine. The sclerae were clear. He was quite dull mentally, and frequently was definitely confused. His response to questioning was very slow. His memory for both recent and past events was blunted. Part of the time his conversation was rational, and part of the time it rambled and had no connection with the questions. He complained of some headache. There was a coarse tremor of the hands, lips, and tongue. There was slight puffiness of the upper eye lids. The neck was not stiff. Hearing and vision were grossly normal. The ear drums were normal. The pupils reacted to light and accommodation. The fundi were negative except for some edema of the retina. There were several carious teeth. The nose and throat were normal. The mucous membranes were pale and moist. The examination of the heart and

lungs revealed no abnormalities. He coughed occasionally. The abdomen was a little distended. The liver was not felt; it percussed one finger's breadth below the costal margin on inspiration. The spleen was not felt and was not enlarged to percussion. The genitalia were negative. There were healed scars of old infections on the legs. Strength was generally weak. The reflexes were equal and active. The plantar responses were equivocal- probably normal. The urine was dark amber, had a specific gravity of 1.014 and contained 2 plus albumin, 20 to 25 red blood cells per high power field, 2 to 3 white blood cells per high power field, and an occasional hyalin, granular, and white cell cast. The hemoglobin was 80 per cent, red blood cell count 3,550,000, white blood cell count 6,350. The differential white count showed segmented forms 78 per cent, stab forms 2 per cent, lymphocytes 12 per cent, monocytes 4 per cent, eosinophils 3 per cent, and basophils 1 per cent. The blood Kahn reaction was negative. The impression on admission was that the patient had malaria which was probably cerebral, and acute glomerular nephritis. Because the nature of the hematuria was not clear, the patient was started on atabrine 0.1 gram 3 times a day by mouth. Because nephritis was suspected and hypertension was present, he was given digitalis 0.3 gram, to be repeated after 4 hours, and to be continued as 0.1 gram 3 times per day. For 12 hours his condition was essentially unchanged. His temperature at 8:00 a.m. on January 23 was 99°F. Around noon he had a generalized convulsion following which he was comatose, but wildly active. His blood pressure after the convulsion was 120/80, and at 5:00 p.m. it was 180/100. The blood urea was 17 mg. per cent and the blood sugar 138 mg. per cent. A blood count showed hemoglobin 8.5 grams and red blood cell count 3,600,000. The total protein was 6.6 grams per cent, albumin 3.5 grams per cent, and globulin 3.1 grams per cent. A blood smear showed one crescent and one ring form of *Plasmodium falciparium*. With those data, it was felt that cerebral malaria was producing most of the clinical picture. He was given quinine dihydrochloride 0.5 gram, with 0.5 mg. of epinephrin borate, in 200 cc. of normal saline intravenously at 2:00 p.m. This was repeated at 8:00 p.m. He was also given 500 cc. of 5 per cent glucose in saline intravenously at 5:00 p.m. Because he continued to thrash around wildly, 20 cc. of magnesium sulphate (25% solution) were administered intramuscularly at 7:00 p.m. He was catheterized (375 cc. urine) at 7:15 p.m. The urine grossly and microscopically was the same as that of the day before. Digifoline, one cat unit subcutaneously, was begun at 7:30 p.m., and was given twice a day for 3 days. 400 cc. of glucose in saline were given intravenously at 8:30 p.m. The patient quieted markedly for about 30 minutes after the magnesium sulphate, but the continuous hyperkinesia returned. Paraldehyde, 15 cc. by rectum, had no effect on this. Despite the renal damage, he was given avertin 60 mg. per kilogram, by rectum, at 11:00 p.m. Before the avertin his condition was poor. Respirations were irregular with periods of apnoea. He was cyanotic. There was divergent strabismus to the right. He was comatose and wildly active. However, his pulse was of good quality, rate 110, temperature 103°F., and blood pressure 180/110. Immediately after the avertin he became quiet, but for a short while respirations

were more irregular. Mucus which had been accumulating in his trachea, increased, and cyanosis increased. He appeared moribund. Tracheal suction with a stomach tube and a 30 cc. syringe finally cleared the mucus, and breathing improved markedly. One hour after the avertin he was quiet, breathing regularly and slowly. Blood pressure was 170/100. A lumbar puncture was performed at 11:15 p.m. The spinal fluid was clear and the pressure seemed low. The Pandy reaction was 2 plus, and no malarial parasites or cells were seen. Only about 2 cc. of fluid were withdrawn. The quinine dihydrochloride, 0.5 gram, with 0.5 mg. of epinephrin borate in 200 cc. of normal saline, were given again at 3:30 a.m. On the morning of January 24, the patient was just beginning to respond by movement when bothered. His temperature was 101.8°F., pulse 108, blood pressure 170/100. His color was good and breathing easy. He was incontinent of urine and feces. The neurological examination was otherwise negative. He was given 1000 cc. of glucose and saline intravenously at 9:00 a.m., and 250 cc. of the same solution at 8:30 p.m. At 12:30 p.m. and 8:00 p.m. he was given quinine dihydrochloride, 0.5 gram, with 0.5 mg. epinephrin borate in 200 cc. of normal saline intravenously. His condition in the afternoon was unchanged. He was still comatose. His temperature was 102°F., and blood pressure 170/100. On January 25, he began to respond a little to questions. His temperature was normal that day. He continued incontinent of urine and feces. The icteric index was 5, red blood cell count 2,950,000, white blood cell count 5,050, hemoglobin 7.5 grams, and the differential white cell count normal except for some shift to the left. His urine contained albumin 2 plus, was loaded with red cells, and showed numerous white cells and occasional casts. His blood pressure was 140/90. He was quiet and slept a good deal of the time.

He was started on liquids by mouth, and given quinine 0.6 gram every four hours when awake, and plasmochin 0.01 gram 3 times a day. His condition remained satisfactory until the afternoon of January 26. At that time he began to have tremors of the facial and arm muscles, and shortly thereafter had a generalized convulsion lasting 5 minutes. Shortly before this, he passed a small amount of fairly bright red blood by rectum. Following the convulsion he remained unconscious for 36 hours. During this time his blood pressure was between 180 to 190/100. At first he thrashed about in bed, but became quiet after the administration of magnesium sulphate, 25 cc. of a 25 per cent solution intramuscularly. On the night of January 26, he was transfused with 500 cc. of citrated blood. He was given quinine dihydrochloride 0.6 gram, and epinephrin borate 0.1 mgm. in 150 cc. of normal saline intravenously 10:30 p.m. January 26, 8:30 a.m. and 8:00 p.m. January 27. He was also given a total of 1000 cc. 5 per cent glucose in saline intravenously. His temperature rose to 102.8°F. at 2:00 a.m. January 27, and continued around 102°F. until the morning of January 28. His neck became quite stiff on the afternoon of January 27, and a second lumbar puncture was performed. The spinal fluid was again under low pressure, and showed a 1 plus Pandy reaction and 6 lymphocytes per c.mm. Culture of the fluid was negative. A blood smear January 27 showed no malarial parasites; the red cells showed

moderate variations in size, and there was much heavy basophilic stippling. On the morning of January 28 he was much improved. He was conscious, seemed to pay attention to conversation and occasionally talked. He was given quinine dihydrochloride 0.6 gram, and epinephrin borate 0.1 cc. in 150 cc. normal saline intravenously at 8:00 a.m. and 5:00 p.m. He took liquids by mouth, and was able to swallow plasmochin 0.01 gram, 3 times that day. He was also given another transfusion of 500 cc. of citrated blood. Urinalysis was essentially unchanged. On the afternoon of January 28 his pulse began to run between 48 and 60 and remained so for about 36 hours. An electrocardiogram taken January 30 showed no abnormality. There was a sinus bradycardia with a rate of 50. On January 29 consciousness had fully returned. He responded slowly to simple questions after a lapse of 5 to 10 seconds. He was still incontinent of urine and feces. He was given quinine dihydrochloride 0.6 gram, with epinephrin borate 0.1 cc. in 150 cc. of normal saline intravenously. He was also given quinine sulfate, 0.6 gram, 4 times by mouth, and plasmochin 0.01 gram, 3 times by mouth. From then on his course was one of steady improvement. His sensorium cleared each day, so that by January 31 he was no longer incontinent. On January 30 he had to be tube fed, but after that took liquids and solids well. His blood pressure gradually dropped to 140/90 on February 3. The edema of the eye lids disappeared by February 1. His temperature did not exceed 100.2°F. after January 30 and was normal from then on. On January 30 he was given quinine sulfate 0.6 gram 4 times, and plasmochin, 0.01 gram 3 times. On January 31 it was noted that his urine was grossly bloody. Before this the color had been dark amber. Microscopically, it was loaded with red cells, and also contained some white cells and cellular casts. It was felt that part of the hematuria was caused by quinine. Consequently, both the quinine and plasmochin were discontinued on that day. Beginning February 1, he was given atabrine, 0.1 gram 3 times a day. The hematuria became less marked each day thereafter, and on February 4 the urine showed only a slight smokey tinge. On January 28 the hemoglobin was 10.0 grams, and the red blood cell count 3,450,000. The blood urea was 19.7 mg. per cent. On January 29 a stool specimen was negative, and a urinalysis was essentially unchanged. On February 1 the hemoglobin was 13 grams, the white count 6,850, the blood urea 15 mg. per cent. A blood smear was negative for malarial parasites. On February 4 his weight was 157½ lbs. A P.S.P. kidney function test showed 15 per cent excretion in 15 minutes and 45 per cent excretion for 1 hour. From February 11 through February 19, the urine showed albumin 1 plus to 2 plus, red blood cells 5 to 15, and very rare white cells casts. On February 16, a P.S.P. test showed no excretion of the dye in 15 minutes, 40 per cent in 30 minutes and 52 per cent in 1 hour. His weight on February 21 was 167 lbs., and his blood pressure was 135/80. Psychiatric consultation by Captain Theodore Lidz, revealed no evidence of any sensorial deficit. His general condition was excellent.


JANUARY
FEBRUARY
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96
97
98
98.6
99
100
101
102
103
104
ATABRINE 0.1 GRAM TID
DIGITALIS
NOON -
2 PM.-QUININE 0.5 GRAM I.V.
CONVULSION AND COMA
11 PM.-MEERIN 60MCM/CC)
3 P.M. -
3.30 A.M.-QUININE 0.5 GRAM I.V.
11 P.M. -LUMBAR PUNCTURE
8 P.M. -
12.30 P.M.-QUININE 0.5 GRAM I.V.
QUININE AND PLASMOCHIN
QUALTY - RESPONDING ALITTLE
QUININE AND
PLASMOCHIN QUALTY
4 P.M. - CONVULSION
10.30 P.M. - QUININE 0.6 GRAM I.V.
AND COMA - MAG. SULPHATE 25 CC (25% SOL.) IM
11 P.M. - 500 CC. BLOOD TRANSFUSION
8.30 A.M. - QUININE 0.6 GRAM I.V.
4 P.M. - LUMBAR PUNCTURE
8.30 P.M. - QUININE 0.6 GRAM I.V.
CONVULSIONS
PLASMOCHIN (0.010 GRAM) THREE TIMES
4 P.M. QUININE 0.6 GRAM I.V.
BLOOD TRANSFUSION
5 P.M. QUININE 1 0.6 GRAM I.V.
9A.M. QUININE
0.6 GRAM I.V.
QUININE AND PLA-
MOCHIN QUALTY
QUININE AND
PLASMOCHIN QUALTY
QUININE AND
PLASMOCHIN
QUALTY - GOOD HEMATOMA
ATABRINE 0.1 GRAM
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ATABRINE 0.1 GRAM T.I.D
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SAME
NO GROSS HEM
ATABRINE

There is some difference of opinion regarding the treatment of malaria. Whether quinine should be used alone, or in courses with atabrine, and exact information concerning the efficacy of plasmochin, have not been definitely determined. At the present time the method of treatment may have to be decided by the available drugs. It is probably safe to say that the usual acute malarial episode may be terminated by either quinine or atabrine, and that in those cases where gametocytes are found in the peripheral blood, plasmochin is also indicated. With the present methods of therapy, there will be a number of relapses of the disease. This number is greatest in infections caused by *Plasmodium vivax*, and least with those due to *Plasmodium falciparum*. In cerebral malaria where oral medication is often impossible, there is a still wider divergence of opinion as to treatment. Dove (3) states that there are no indications for the intramuscular or intravenous use of quinine. He advises the intramuscular injection of atabrine when the oral dose cannot be swallowed, retained or absorbed, with a temperature of 104 or over, with pernicious types, and when there is failure of remission of fever under oral treatment. If atabrine is not available for injection, he uses quinine intramuscularly. In a moribund patient whose circulatory efficiency is very poor and cannot be improved by fluids and stimulants, he then advises that atabrine be given intravenously. During 14 years in the American tropics, Dove has seen 4 deaths from acute malaria, and three of these occurred during or immediately after intravenous injection of quinine. However, Dove is not specific concerning the toxicity of intravenous quinine. He mentions that it may precipitate an attack of blackwater fever, and that it may suddenly liberate into the blood many toxins from the sudden killing of many parasites. Other authorities (4) do not share the opinions of Dove. Stitt writes that all authorities recognize conditions in which quinine given intravenously is a necessity. He considers that this method is indicated in the comatose and algid types of malaria. Goodman and Gilman (5) state that intravenous injections of quinine are dangerous, and should be reserved for such an emergency as severe cerebral malaria. They evidently are mainly concerned with the cardiovascular collapse that may follow such an injection. All of these writers mention the occasional case in which there is serious hypersensitivity to quinine, and all agree that quinine given intramuscu-

larly is too apt to produce sterile abscesses. From a consideration of these facts, and from a very limited experience, it is my opinion that intravenous quinine is the treatment of choice in the patient who is comatose from cerebral malaria. Atabrine given intramuscularly is not effective as rapidly, has been reported to precipitate blackwater fever, can cause necrosis of the liver and sterile abscesses. Needless to say, the quinine must be given well diluted and very slowly. Not more than 2 grams should be administered within 24 hours. Oral medication should be commenced as soon as the patient is able to take it. The addition of a small dose of epinephrin to the intravenous solution may aid in the prevention of a serious drop in blood pressure.

The renal changes exhibited by this patient are of interest. Stitt (1) says that albuminuria is common in aestivo-autumnal attacks, and that nephritis has been reported in about 2 per cent of cases in some series. He quotes Sinton and Lal as finding albuminuria in 14 per cent of 467 cases. He also says that MacFie, Lambers and Manson-Bahr lay stress on the reports of nephrosis as a complication of malaria. Stitt describes cloudy swelling and small hemorrhages in the mucosa of the kidney pelvis and calyces. In this patient the combination of hematuria, albuminuria, cylindruria, hypertension and periorbital edema make me believe that there must have been diffuse glomerular damage. The increase in hematuria that occurred during treatment with quinine and disappeared following the withdrawal of the drug, suggests that the quinine was responsible for this increase. Goodman and Gilman (5) state that renal damage may be caused by quinine, and hemoglobinuria has occasionally appeared in non-malarial pregnant women taking it. This patient did not develop hemoglobinuria and there was no evidence of much hemolysis of the red blood cells. Avertin also may increase preexisting kidney damage, but in this case it does not seem to have done so. It is barely possibly that the patient had an acute glomerular nephritis secondary to infections on the legs, but this too seems unlikely. My opinion is that he had a true malarial nephritis, i.e., the glomerular capillaries were filled with enough parasites to produce the clinical picture of acute nephritis, and that the continuing urinary abnormalities are due to damage of these capillaries by the parasites. It is obvious that such an opinion cannot be proved and is open to contradiction. The idea that quinine was partly

responsible for the gross hematuria rests on stronger evidence, because the urine lost its bloody color shortly after the drug was discontinued. Whatever the pathogenesis of the kidney lesion, this patient presented the clinical picture of acute glomerular nephritis occurring during the course of cerebral malaria produced by Plasmodium falciparum.

SUMMARY

A case of severe cerebral malaria due to Plasmodium falciparum has been described. Recovery followed the use of quinine intravenously.

Urinary and blood pressure findings consistent with those of acute glomerular nephritis were present. These findings decreased steadily during the period of observation.

I wish to express my thanks to Lieut. Colonel B. M. Baker and to Major A. J. Schaffer, of the 18th General Hospital, for their aid in the treatment of this case and in the preparation of this paper.

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LYMPHOCYTIC CHORIOMENINGITIS

Report of a Laboratory Infection

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Because of the relatively small number of reported cases of laboratory infection with the virus of lymphocytic choriomeningitis in which the virus has been isolated, the following case report is submitted as an additional example of accidental infection. A brief account is also given of the isolation of the virus with the subsequent immunological studies. A complete discussion of the entire subject of lymphocytic choriomeningitis is contained in the excellent paper by Farmer and Janeway (1). Since the publication of their article several additional cases of the disease, with isolation of the virus, have been reported in the American literature (2, 3, 4).

CASE REPORT

G. S. H. (J. H. H. #274369), a 30 year old white, single physician, who was engaged in virus research, entered the Johns Hopkins Hospital on the evening of October 28, 1942, with a chief complaint of anorexia and weakness of two days' duration.

The family history was noncontributory. The past history revealed that the patient had had a chronic otitis media on the left since infancy, and had suffered measles and chickenpox during childhood. At the age of eighteen years he had a mild case of whooping cough, but there was no history of scarlet fever, mumps, or diphtheria. At the age of twenty-one he contracted infectious jaundice, but was ill for one week only. During the year previous to admission the patient had been working in a bacteriological laboratory, and from time to time had experimented with sputum and blood samples from patients with "atypical pneumonia."

Eighteen days before admission, October 10, 1942, the patient unwittingly flamed what was thought to be an ordinary glass tube of a 10 per cent suspension of virulent guinea pig spleen, containing the WE (Rivers) strain of lymphocytic choriomeningitis virus. The tube was made of heavy celluloid, however, and exploded. Three-fourths of the contents were sprayed about, some of the material spattering on the patient's head. A mask and gown were worn at the time, and, although the patient did not wear glasses, he was not conscious of any of the material getting

[1] Henry Strong Dension Scholar for 1943.

into his eyes. The hair on the head was immediately washed with 70 per cent alcohol. The remainder of the contents of the tube was injected intraperitoneally into each of two guinea pigs. One of these became ill and was sacrificed on the fifth day, and the other died on the eighth day, following a period of weight loss, roughing of the coat, and fever.

On October 17, 1942, *eleven days before admission*, and a week after the accident, the patient developed a typical "cold" consisting of coryza and cough, producing fairly large amounts of mucopurulent sputum. Despite these symptoms which persisted for four or five days, there was no malaise, anorexia, or feverishness. A residual dry hacking cough persisted for a week, and subsequently increased in severity.

Thirty-six hours before admission, chilly sensations were noted, and anorexia and weakness made their appearance. The leukocytes at this time were 5600 per cubic millimeter. The patient went to bed that night, slept fitfully, and the chilly sensations increased in frequency, occurring particularly on moving around in bed. On the morning of entry, he noted slight soreness of the head without headache, pain on lateral deviation of the eyes, and soreness of the neck muscles, without any evidence of rigidity. There was likewise some tenderness of the muscles of the back and extremities. A nonproductive cough became quite bothersome. There was extreme fatigue at the slightest exertion, and anorexia became outstanding. No other gastrointestinal symptoms were noted. He remained in bed that day, without subjective improvement. In the evening he was seen by a physician who found his oral temperature to be 102.5°F., and admission to the hospital was advised.

On admission, the patient was found to have a temperature of 103.2°F., (rectal), a pulse of 80, respiratory rate of 20, and the blood pressure was 130/70. He appeared somewhat prostrated, but not seriously ill, and was perfectly rational and well oriented. The skin was warm and moist. The palpebral conjunctivae were quite red, and there was minimal injection of the bulbar conjunctivae. The extraocular movements were well performed, although causing slight orbital pain, and there was no photophobia. The pupils and fundi were normal. There was chronic otitis media on the left. The nasal and pharyngeal mucous membranes were injected. The neck was supple and there was no significant adenopathy. The heart, lungs, and abdomen were within normal limits. There was slight tenderness of the muscles of the extremities. The neurological examination was entirely negative.

A blood examination on admission showed the leukocytes to be 7700 per cubic millimeter, with a differential count of 5 per cent juvenile cells, 55 per cent polymorphonuclears, 1 per cent eosinophils, 26 per cent lymphocytes, and 13 per cent monocytes. The hemoglobin was 14.6 grams, the volume of packed red cells 47 cc. and the icteric index 8. The urine and stool examinations were negative. A blood culture on admission showed no organisms, and the Eagle and Wassermann tests were negative. A culture of the throat revealed "normal throat flora."

Course (See Chart 1). By the third hospital day, October 30, 1942, the patient's temperature had returned to normal, and the pulse averaged 60. Though insomnia persisted, the malaise, pain on moving the eyes, and muscle soreness diminished rapidly, and the appetite improved. On the second hospital day, October 29, 1942, a guinea pig was injected with 2.0 cc. of the patient's whole blood. (See below.)

On November 3, 1942, the sixth hospital day, the patient developed a transient pleuritic pain in the right anterior chest and shoulder, worse on coughing and deep breathing, but unaccompanied by chills, fever, or abnormal physical signs. A roentgenogram of the chest taken at the time showed the lungs to be clear. November 4, 1942, the patient was discharged, asymptomatic except for rather marked weakness on mild effort. The leukocytes had varied between 6100 and 7700 per cubic millimeter.

That same night he took an eight hour train trip to his home during which time he slept soundly. He awakened feeling quite well, but towards mid-afternoon he once more felt weak even though resting, and lassitude was pronounced.

The following morning, November 6, 1942, the hacking cough recurred, and marked malaise, chilly sensations, sweating, and extreme weakness developed. The symptoms at this time were more severe than during the original illness. That evening the temperature rose to 103.2°F. by mouth and he became nauseated and vomited once, but the soreness of the neck muscles and headache were conspicuously absent. The oral temperature varied between 102°F. and 103°F., and the pulse ranged from 55 to 70. On November 7, 1942, the second day of exacerbation of symptoms, physical examination was not remarkable except for diminished breath sounds and the presence of a few fine persistent râles in a small area high in the right axilla. These signs persisted for only three days, without the development of a friction rub or signs of consolidation, but unfortunately x-ray examination was not possible at the time.

The temperature returned to normal by the end of the fourth day, and the patient remained afebrile thereafter. There was a gradual return of well-being until, by the end of the third week, only a slight residual afternoon and evening weakness persisted. A chest plate at the time showed no abnormalities.

There was a total weight loss of about seventeen pounds, and normal activity with exercise was not satisfactorily resumed until eight weeks after the original laboratory exposure. It may be of interest to note that the patient suffered a mild attack of infectious mononucleosis six months later, but there is no evidence to assume that this was in any way related to the above infection.

The following studies were made of a virus obtained from the blood of the patient on October 29, 1942. This virus will hereafter be referred to as the "HH" virus.

A. *Isolation.* On October 10, 1942, the patient was initially exposed

to the WE (Rivers) strain of lymphocytic choriomeningitis virus.[2] On October 17, 1942, one week after exposure and at the time of a prodromal "cold," a guinea pig was inoculated intraperitoneally with 2.0 cc. of the patient's whole blood. The pig remained living and well for twenty-one days and was discarded.

On October 29, 1942, the second day of the acute febrile illness, 2.0 cc. of the patient's blood was injected intraperitoneally into a guinea

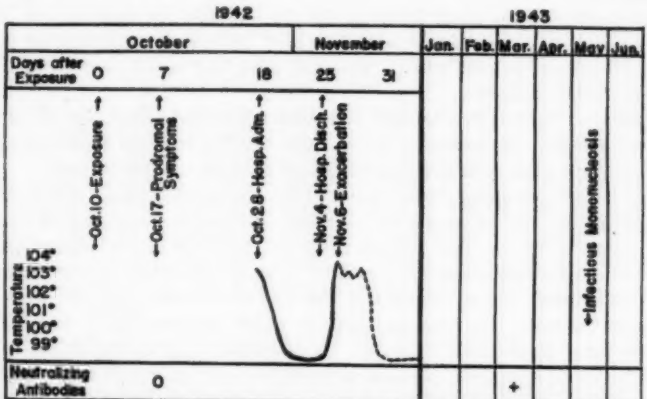

CHART 1. SHOWING THE CLINICAL COURSE OF THE INFECTION SUBSEQUENT TO EXPOSURE, AND ITS RELATIONSHIP TO THE ISOLATION OF A VIRUS FROM THE BLOOD AND TO THE DEVELOPMENT OF COMPLEMENT-FIXING AND NEUTRALIZING ANTIBODIES

pig. This animal developed an elevation of temperature on the fourth day, with subsequent weight loss, shaggy coat and emaciation, and died eleven days after inoculation. Shortly after death, the organs were removed aseptically, and the lung was found to be studded with tiny hemorrhagic areas. Ten per cent suspensions of the brain and of the spleen were made in saline, and each suspension was immediately injected into mice and guinea pigs. Of the three mice

[2] This strain was originally obtained through the kindness of Dr. Harry Eagle of the Department of Medicine, Johns Hopkins University, Medical School.

inoculated intracerebrally with 0.03 cc. of the spleen suspension, two died on the second day, presumably from trauma, while the third mouse, as well as the four mice inoculated intracerebrally with brain suspension, became ill on the sixth day, and died on the seventh to eighth day with characteristic convulsive seizures. Histological sections of the mouse brains and lungs showed, in the former, perivascular round cell infiltration, and, in the latter, an interstitial type of pneumonia.

Two guinea pigs, one of which had received 2.0 cc. of the brain suspension intraperitoneally, and the other of which had been similarly inoculated with 4.0 cc. of the spleen suspension, both developed symptoms identical to those of the original guinea pig, and died in nine days. The lungs at postmortem showed patchy areas of hemorrhagic and brownish consolidation grossly, and on microscopic section showed an interstitial type of pneumonia with mononuclear cell infiltration.

Subsequently, six intracerebral mouse passages were made, using 10 per cent brain suspensions in saline as the inoculum.[2] All of the mice died in from seven to ten days. Three further guinea pig passages were made by intraperitoneal injection of brain, spleen, or lung suspensions, and all of the pigs, following the development of typical symptoms, died from eight to eleven days after inoculation. Third passage guinea pig liver, lung, and heart emulsions were inoculated into three mice intraperitoneally in amounts of 0.25 cc. Two of the three mice in each group survived and were found subsequently to be immune to intracerebral injection of 0.03 cc. of a 10^{-1} dilution of the WE (Rivers) strain of lymphocytic choriomeningitis virus. Four normal control mice inoculated intracerebrally with a similar amount of the WE strain died in eight days.

In addition to the animal experiments, the chorioallantoic membranes of developing chick embryos were inoculated with virulent mouse brain emulsions, but no definite pathological changes were noted. This is in agreement with previous reports (14, 15). Allantoic fluid was found to be inadequate passage material as, on the third egg passage, we were unable to demonstrate infectivity for mice of either the fluid or the chorioallantoic membrane. Storage of the fluid between

[2] At a later date the saline was replaced by "Z" solution (5) in preparing the inocula.

passages at −30°C. may have influenced the results, although it is to be noted that virulent mouse brain retained its infectivity for at least six months when stored at this temperature.

Organ suspensions were routinely cultured in Brewer's liquid thioglycollate medium before each passage and were found to be sterile. Blood agar plates showed no growth, and no pleuropneumonia-like organisms were found in passage material when seeded on 20 per cent horse serum starch dextrose agar (Difco).

The presence of latent lymphocytic choriomeningitis virus infection in the stock animals tends to be ruled out by the fact that all the control animals died when inoculated with a standard virulent strain of the virus. Likewise, during the course of the studies, mice were occasionally injected with 0.03 cc. of a 10 per cent suspension of normal mouse brain intracerebrally, without becoming ill.

Neutralization Tests. A. The following test was set up to determine whether the patient had developed neutralizing antibodies to the virus (HH) which had been isolated from his blood, and, in addition, to determine whether this virus would be neutralized by the hyperimmune serum of a guinea pig immunized with a known strain of lymphocytic choriomeningitis virus.[4] The test was carried out according to the method of Armstrong and Dickens (18) except that the sera used were diluted 1:5 throughout. The procedure, in brief, consisted of inoculating a mouse intracerebrally with 0.03 cc. of HH virus. The mouse, becoming ill on the sixth day, was sacrificed, and the brain was removed aseptically. A 10 per cent brain suspension was made in "Z" solution (5) and was centrifuged at 3000 r.p.m. for ten minutes to remove the gross cellular debris. From the supernatant fluid which was a 10^{-1} dilution, dilutions of 10^{-2} and 10^{-3} were made, and 0.25 cc. of each dilution was mixed with 0.5 cc. of a 1:5 dilution of the sera to be tested. These mixtures were incubated for four hours at 37°C. and 0.03 cc. of the various serum-virus dilution mixtures was injected intracerebrally into each of five mice. The results are indicated in the chart below.

Chart 2a shows that a specimen of the patient's serum drawn on the day of exposure, did not neutralize the virus, in contrast to the

[4] This serum was kindly supplied by Dr. Lewis Thomas of the Rockefeller Naval Medical Research Unit.

specimen obtained on the 115th day of convalescence, which gave definite though partial neutralization. Neutralization of the HH virus by the known immune guinea pig serum was complete.

B. A known strain of lymphocytic choriomeningitis virus (WE) was then tested against the same sera from the patient as those used above. The results were virtually identical, as shown in Chart 2b. The set of experiments serves not only to identify the virus (HH) but also to show that this virus produced protective antibodies in the patient.

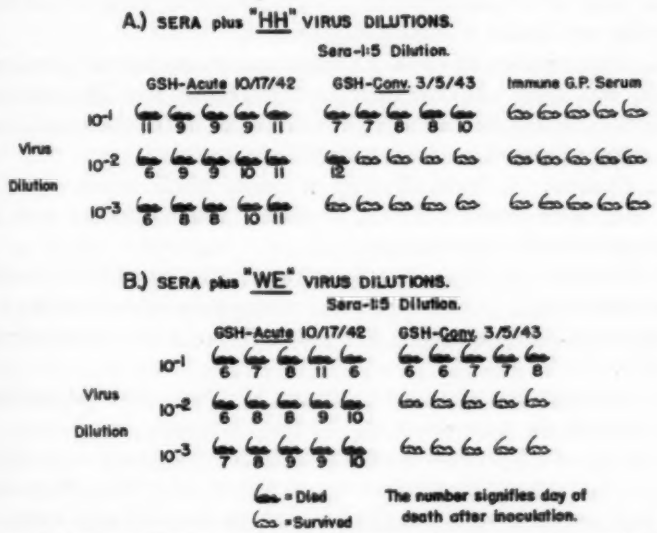

CHART 2. SHOWING RESULTS OF NEUTRALIZATION TESTS WITH PATIENT'S SERA AND LYMPHOCYTIC CHORIOMENINGITIS IMMUNE GUINEA PIG SERUM, AGAINST THE VIRUS FROM THE PATIENT (HH) AND THE KNOWN LYMPHOCYTIC CHORIOMENINGITIS VIRUS (WE)

One part of virus dilution mixed with two parts of 1:5 serum, incubated 4 hours at 37°C.; 0.03 cc. of each mixture inoculated intracerebrally into 5 mice.

The mice which survived both neutralization tests were injected with a 10^{-1} mouse brain suspension of HH virus 30 days later. These all succumbed, demonstrating a lack of immunity.

Complement Fixation. A. Antigen—This was prepared according

to the method outlined by Smadel, Baird, and Wall (6), except for the fact that no ultracentrifuge was available to separate the soluble specific antigen from the virus. The Seitz filtrate of the guinea pig spleen suspension, therefore, was presumed to be infective. The antigen was stored at −30°C., and frequent freezing and thawing did not diminish its activity. This antigen was not anticomplementary even in undiluted form, but the addition of formalin to a concentration of 0.4 per cent in an attempt to inactivate the virus, rendered the antigen too anticomplementary for use. Heating at 52°C. in the water bath for 90 minutes completely destroyed all antigenic activity but did not render it anticomplementary.

B. Complement—2½ units of complement in the form of guinea pig serum was used. This amount of complement was 2½ times the amount necessary to cause complete hemolysis of the sheep red blood cell suspension used as the hemolytic indicator.

C. Protocol. 1. Serial dilutions of serum (whole serum, 1:2, 1:4, 1:8, etc.) were tested in 0.2 cc. amounts. These dilutions were inactivated at 63°C. for three minutes.

2. To each tube 0.2 cc. of 1:3 antigen and 0.2 cc. of 1:10 complement were added. (The amount of amboceptor used was adjusted to permit complete hemolysis by 0.2 cc. of 1:25 complement in 30 minutes at 37°C.)

3. The tubes were placed in the icebox (4°C.) for one hour and then incubated in the water bath (37°C.) for one hour.

4. 0.4 cc. of 1.5 per cent sensitized sheep red blood cells were added and the reading was made when the second control tube, containing one half the amount of complement used in the test, was clear.

5. Each setup contained an antigen control (lacking serum) and a complement control (lacking antigen and serum), as well as a serum control (lacking antigen) in each dilution.

6. The titer of a given serum is expressed in units as the highest dilution which gave a positive result. Thus a serum positive in a 1:4 dilution and negative in 1:8 is said to have a titer of four units, while a serum positive in 1:64 dilution and doubtful in 1:128 was arbitrarily given an interpolated titer of 96 units.

Sera were taken from the patient at intervals up to eight months after infection, and each sample was tested on at least six different

occasions. The titers were relatively consistent throughout, usually varying by no more than one two-fold dilution, except for the serum drawn February 2, 1943, which showed a steady decrease in titer from 192 units (repeated on two occasions) to 8 units. Simultaneously during these tests, conducted over a six-month period, 155 other sera from 84 patients were tested, most of which were from patients with atypical pneumonia. Only two of these sera had a titer of more than 4 units, and these had a maximum of 8 units.

TABLE I

	10/10/42	10/17/42	10/29/42	1/6/43	2/7/43	3/5/43	6/14/43
Units	0	0	0	24	192	16–24	12–24

COMMENT

A. *Mode of Infection.* It is often difficult to determine the exact moment and mode of infection of laboratory workers who are in close contact with infectious agents over a protracted period of time. In this particular instance, however, the initial exposure was a massive one, and a known incubation period of 17 days coincides well with those reported elsewhere (1, 8). The actual route of infection is problematical, but appears limited to one or more, of three possibilities, the skin, the conjunctivae, or the respiratory tract. Shaughnessy and Zichis (9) have demonstrated experimental infection in guinea pigs by application of the virus to the unbroken skin, and it is conceivable that such might happen in human beings. Milzer and Levinson discussed this possibility (3), but they tended to favor the bite of infected monkey lice as the source of infection in their case.

Lepine and Sautter's patient (8) developed clinical infection following accidental eye contamination, even though argyrol had been instilled, but there had been actual penetration of the conjunctiva by an infected glass fragment. Another laboratory worker (3) contaminated his eye with infectious material but, after rinsing with boric acid solution, failed to develop either a clinical or serological response. In our own case, conjunctival contamination was a possibility, but the patient had no recollection of any material spattering into his eye.

Infection via the respiratory tract cannot be proven, but it seems

logical to assume that, under the circumstances, an ordinary gauze mask provides relatively little protection. It is of interest, therefore, that, although working for eight months with infectious material, and without strict precautions, three other members of the laboratory staff failed to show either clinical or serological evidence of infection with the virus of lymphocytic choriomeningitis.

B. *Clinical Course.* Infection of the meninges in the patient cannot be excluded, since no lumbar puncture was performed, and, although the headache was slight and of short duration, and was unaccompanied by a stiff neck, there is no definite proof that the disease failed to involve the central nervous system. A lack of headache characterized the proven cases of systemic disease without meningitis (7, 10, 11).

Whether or not an inflammatory reaction of the lung developed in our patient is likewise debatable, since no x-rays were available at the time that signs were present. The definite physical signs in the chest, however, were confirmed independently by two competent observers. Respiratory symptoms are apparently rare except in the prodromal period, and most of the protocols of the proven cases make no mention of cough, pain in the chest, or of abnormal signs in the lungs. However, in monkeys, guinea pigs, and mice, pulmonary lesions are present (1, 13), and symptoms or postmorten findings consistent with lung involvement have been reported in human beings (11, 12, 16). It may be stated that in the present case, the respiratory symptoms were prominent enough to confuse the clinical picture, despite the known laboratory exposure. The original clinical impression was "La Grippe." Atypical pneumonia was strongly considered, and the hospital discharge diagnosis was "Bronchitis of undetermined etiology."

C. *Complement Fixation.* The antigen used for the complement fixation tests was, as mentioned above, presumably a "live" antigen, and no attempt was made to inactivate it by allowing it to stand in the ordinary icebox over a long period of time. Control tests indicated that there was no significant loss of antigenicity on repeated freezing to −30°C. and subsequent thawing, and thus the decrease in complement fixing titer noted in the serum of February 7, 1943, reflected a change in the serum and not in the antigen. The serum in question

had been frozen and thawed at least six times, and it was noted that a large amount of precipitate formed with each thawing. This was centrifuged out (3000 r.p.m. for ten minutes), and it is conceivable that some of the antibody was removed in the sediment. All the other sera tested were relatively free from precipitate.

It is interesting to note that the complement fixing titer, except for one sharp rise, remained almost constant, and the titer at eight months was virtually the same as that at three months after exposure. This is in contrast to the usual findings in animals and man (1, 17), but it is in keeping with the results of Milzer and Levinson (3) who found a constant titer over a two-year period. The persistence of complement fixing antibodies may be due to (1) persistent infection, that is, a virus-carrier state, (2) complete subsidence of infection with persistent circulating antibodies, or (3) continued contact with the virus; although if the latter were responsible, one would expect similar evidence of at least subclinical infection in the other exposed members of the laboratory staff.

SUMMARY

A laboratory infection with the virus of lymphocytic choriomeningitis is reported which, following an incubation period of 17 days, gave rise to an infection primarily systemic in character. The virus was isolated from the blood of the patient during the acute stage. Neutralizing and complement fixing antibodies were demonstrated during convalescence.

We wish to express grateful appreciation to Dr. Harry Eagle for invaluable aid and criticism during this study.

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EFFECT OF AMPHETAMINE (BENZEDRINE) SULFATE UPON HIGHER NERVOUS ACTIVITY

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I. Animal Experiments

In the past few years amphetamine (benzedrine) sulfate[1] has been recommended for an extensive variety of conditions in all fields of medicine. Although it has been widely used as a cerebral stimulant, little is known about the dynamics of this action.

Since the quantitative determination of conditioned reflexes has been shown to be an accurate index of cerebral functioning (1), this method was employed in the study of the effect of amphetamine sulfate. Similar experiments on the action of alcohol, caffeine, sodium bromide, chloral hydrate and amytal (2, 3) have already been published.

Though some experimental work concerning the effect of amphetamine on cerebral function has been reported, no comprehensive study has been made. Skinner and Heron (4) studying its effect on conditioned phenomena in white rats trained to receive food at four minute intervals by pressing a lever, reported that after 0.5 mgm. of amphetamine was given, there was a restoration of the conditioned reflex which had previously been extinguished by lack of reinforcement. This was interpreted as evidence that the drug caused the rats "to release energy at a higher than normal rate whether in a state of inhibition or not." They found also that amphetamine was a more powerful destroyer of inhibition than caffeine.

Wentink (5), also using rats conditioned to press a lever, found a diminution of internal inhibition with 0.5 mgm. but at the same time found that the rate of conditioning in four rats was increased 142 per cent.

Minkowski (6), using the same dose of 0.5 mgm. in white rats, showed that his animals failed to learn a Stone maze as readily as a

[1] The benzedrine was furnished through the courtesy of Smith, Kline and French Co.

control group. The animals appeared sluggish and there was definite retardation of general performance. Dispensa and Barrett (7) found that performance of albino rats was poorer in the running of a wading maze after the intraperitoneal injection of 0.25 to 1.0 mgm. per kilogram.

Other effects of the drug on the nervous system have been reported, such as those on sexual reflexes and on spontaneous activity. That on sexual reflexes has never been clearly demonstrated, although Schimmenti (8) makes the statement that amphetamine sulfate tends to "have an inhibitory effect on erection by decreasing the vascular tone through stimulation of the vasoconstrictor fibers of the nervi erigentes." Other reports without controls claim increased libido in man (9). By quantitatively measuring the unconditioned sexual reflexes under controlled conditions in dogs, it was possible in this study to demonstrate clearly a change in these reflexes after administration of the drug.

Experiments in animals have shown definite pressor effects and stimulation of respiration (9). Reference has frequently been made to the decrease in appetite and salivary secretion both in animals and human beings. For a more complete discussion of the physiologic actions of this drug, the reader is referred to the review of Ivy and Krasno (9), and for its clinical applications to the work of Myerson (10).

METHODS

1. CONDITIONED SECRETORY REFLEX

The method used in this study to measure conditioned salivary secretion has been described in detail by Wolff and Gantt (2, 3, 12).

The dog was placed in the experimental camera which was designed to prevent stimuli other than the conditioned stimuli from interfering with the tests. The duct of one of the parotid glands had previously been transposed so that it opened on the cheek. Over the opening of the duct was placed a small metal cup, which was attached securely with wax of low melting point. This cup was connected by rubber tubing to a manometer, the entire system being filled with water. All the salivary secretion from that parotid duct could then be measured from outside the experimental camera on the manometer.

The conditioned stimuli used were auditory; *i.e.*, metronomes of various frequencies and a bubbling sound, and were located within the chamber. The conditioned stimulus, when excitatory (reinforced), began ten seconds before the

unconditioned stimulus (food), and continued for five seconds after the food was given. In one out of every six determinations, the time between the conditioned and unconditioned stimuli was extended to thirty seconds so that a more accurate measure of the conditioned secretion might be obtained. The conditioned secretion is that parotid salivary secretion which occurs between the beginning of the conditioned stimulus and the food stimulus. The time between the occurrence of the conditioned stimulus and the beginning of the conditioned secretion is the latent period of that secretion. The parotid secretion occurring for one minute after the unconditioned stimulus was taken as the unconditioned secretion. The conditioned stimulus, when inhibitory, was given for a period of thirty seconds and was not reinforced.

Two dogs with well-established secretory reflexes were used in the study of the effects of amphetamine sulfate upon the conditioned and unconditioned secretory reflexes. *Billy* was a stable male bull terrier, weighing about 16 kgm., about 12 years of age. Having been an experimental animal in the Pavlovian Laboratory for 10 years before this experiment was begun, his quantitative conditioned reflexes had been measured frequently so that a stable level was obtained. Billy had a well-formed strong excitatory, secretory reflex to one conditioned stimulus (bubbling) reinforced by an unconditioned stimulus of three biscuits (12 gm.) and had a weak excitatory, secretory reflex to another conditioned stimulus, M20 (metronome with a frequency of 20 beats per second), reinforced with one-half a dog biscuit (2 gm.).

Sechs was a male dog of stable type about 6 years of age, weighing about 23 kgm. He had a well formed strong excitatory, conditioned secretory reflex to the conditioned stimulus (bubbling) reinforced by three biscuits, and an inhibitory conditioned secretory reflex to M40, which was not reinforced.

On each experimental day, the dog was placed in the camera, where a series of twelve conditioned stimuli in alternation were given, reinforced by the unconditioned stimuli if excitatory and not reinforced if inhibitory. Readings were made of the quantity of conditioned secretion and its latent period, and the quantity of unconditioned secretion. Observations were also made of the orienting reflex, the motor reflex to the conditioned stimulus, the activity of the dog, and secretion between readings. Three to five minutes were allowed between each set of readings.

On alternate experimental days, the dogs were given amphetamine sulfate, and after a twenty minute delay, readings were begun and finished approximately 105 minutes after giving the drug. On the other experimental days the same routine was performed without drug.

Amphetamine sulfate was administered orally in the form of 10 mgm. tablets. Twenty mgm. were administered to Billy and 20 to 30 mgm. to Sechs.

The duration of the effect was studied in Sechs. After administration, a set of four conditioned stimuli were tested in the camera every two hours until no effect was noted. It has already been shown (11) that such a repetition by itself will not influence the quantitative measure of the secretory reflexes.

2. CONDITIONED MOTOR REFLEX

Conditioned motor reflexes consisting of flexion of the left foreleg to avoid an electric shock were established in two dogs. The conditioned stimulus was a bell or a metronome given three seconds before the unconditioned stimulus (an electric shock) was given, and overlapped the unconditioned stimulus by one second.

Flexion of the left foreleg after the conditioned stimulus and before the shock was the conditioned motor response. The percentage of conditioned responses to a series of conditioned stimuli was determined as well as the latent period of the conditioned response. Twenty conditioned stimuli were given on each experimental day, with intervals of about 30 seconds between them.

Two dogs were used in studying the effect of amphetamine sulfate on the conditioned motor reflex. *Vesal* was a male, collie dog, weighing 11 kgm., about 5 years of age, with a well established excitatory conditioned motor response to, M40. *Conscription* was a male police dog, weighing 12 kgm., about 2 years of age, with a well developed excitatory conditioned reflex to M100 and an inhibitory conditioned reflex to M60.

On alternate experimental days the dog was given twenty mgm. of amphetamine sulfate orally, and after a delay of one hour the readings were begun and continued for about 30 minutes. On the other experimental days the procedure was repeated without the drug.

To determine the duration of the effect, a set of ten conditioned stimuli were given to Vesal at intervals of two hours after the drug until no effect was apparent.

3. CONDITIONED AUTONOMIC SYSTEM

While the readings on the conditioned motor and secretory reflexes were made, cardiac and respiratory rates were occasionally taken by means of an electrocardiograph and a pneumograph.

4. UNCONDITIONED SEXUAL REFLEXES

After the completion of the readings on the conditioned motor and secretory reflexes on Billy, Sechs and Conscription, measurements were made of the latent period of erection, the duration of erection, and the latent period of ejaculation to a constant sexual stimulus. (For a description of this method see Gantt (12).

5. CALCULATIONS

The readings obtained in these experiments were tabulated in two groups, those taken under control conditions and those one to two hours after the oral administration of amphetamine sulfate. Averages and the standard deviation of these averages were calculated. The difference between the control average and the amphetamine average was obtained, and the significant ratio of this difference calculated, taking into account the fact that measurements were made on the same dog. When this significant ratio is equal to two, the chance that the difference was a chance variation is one in twenty.

RESULTS

The conditioned secretory reflex was measured in two dogs, Billy and Sechs. The effect of amphetamine in the dose of approximately 1.0 mg. per kgm. of body weight depended upon the nature of the conditioned stimulus. With the quantity of conditioned parotid secretion as a measure of intensity, it was found that a strong excitatory stimulus was not greatly altered, a weak excitatory stimulus was moderately increased and an inhibitory stimulus became weakly excitatory (see Table I). For the sake of clarity in all tables only the

TABLE I

Effect of Amphetamine Sulfate upon Conditioned Salivary Secretion

TOTAL CONDITIONED SECRETION					STATISTICS			
Dog	Conditioned stimulus	Control *mean*	Amphetamine *mean*	Change after amphetamine	No. of control readings	No. of amphetamine readings	Signif. ratio of change	Change of ratio: $\frac{\text{Total cs}}{\text{Total US after drug}}$
		units	*units*	*per cent*				*per cent*
Billy	Strong excitatory (Bu)	92.5*	104.7	+13	30	15	0.9	+23
Sechs	Strong excitatory (Bu)	62.5	56.5	−10	30	17	1.0	+19
Billy	Weak excitatory (M20)	46.9	74.7	+59	29	15	2.4	+72
Sechs	Inhibitory (M40)	24.4	37.4	+53	34	22	1.1†	—

*1 unit = 0.00167 cc. of salivary secretion.

† Although this significant ratio appears to be too small to permit a conclusion that there was an increase in conditioned reflex secretion, the fact that the inhibitory type of curve became excitatory in shape when the secretion was plotted in Figure 1 is sufficient to warrant such a conclusion.

cs = conditioned stimulus; US = unconditioned stimulus.

results obtained with the conditioned secretion occurring during 10 seconds are given. In every case the thirty second readings showed about the same quantitative change in the same direction as the ten second readings.

From the data obtained it is possible to derive a quantitative measure of the differentiation between a strong excitatory and a weak excitatory conditioned stimulus, or between a strong excitatory and an inhibitory conditioned stimulus by determining the normal ratio of

strong to weak or strong to inhibitory. Any difference in these ratios after the drug can be taken as a measure of the change in differentiation. An increase in this ratio represents a loss of differentiation and, if the ratio becomes unity, there is complete loss of differentiation. Any decrease in this ratio represents an increase in differentiation. Similar calculations can be performed with the data obtained from the conditioned motor defense reflexes, but here the results are not as reliable because the movements can not be registered with the same quantitative accuracy as is the parotid secretion.

Each of three dogs having two different salivary conditioned reflexes (making possible a study of change in differentiation) showed that

TABLE II

Loss of differentiation after amphetamine sulfate as shown by both conditioned secretory and conditioned motor defense reflexes

DOG	CONTROL RATIO*	RATIO AFTER DRUG	DIFFERENCE (EQUALS LOSS IN DIFFERENTIATION)
	per cent	*per cent*	*per cent*
Billy	50	71	+21
Sechs	39	66	+27
Connie	1	14	+13

* Ratio with Billy and Sechs = $\frac{\text{total conditioned secretion with inhibitory or weak excitatory stimulus}}{\text{total conditioned secretion with strong excitatory stimulus}}$

Ratio with Connie = $\frac{\text{per cent of foot withdrawals to inhibitory stimulus}}{\text{per cent of foot withdrawals to excitatory stimulus}}$

there was a definite decrease in differentiation as measured by an increase in the ratio mentioned above (Table II, fig. 1).

These changes are demonstrated in Figure 1, which is a graph of the conditioned parotid secretion as it varies with the time after the conditioned stimulus is given. Amphetamine affected 1) the secretory curve of the strong excitatory conditioned stimulus by shifting the curve towards the left—shorter latent period (fig. 2, table III) but changing only slightly the height of the curve (total conditioned secretion), and 2) the secretory curve of the inhibitory stimulus by changing it from a straight line parallel to the horizontal axis to a curve which resembles the excitatory stimulus; i.e., by converting inhibition into excitation.

The conditioned motor defense reflex was measured in two dogs, Vesal and Conscription. Amphetamine decreased the incidence of foot withdrawals to an excitatory stimulus and increased the incidence

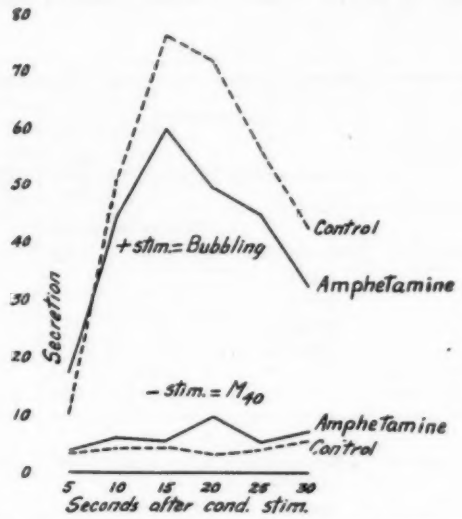

FIG. 1. EFFECT OF AMPHETAMINE SULFATE ON SIZE OF CONDITIONED SECRETORY REFLEXES

TABLE III

Effect of amphetamine sulfate upon the latent period of conditioned secretion

DOG	STIMULUS	TOTAL CONDITIONED SECRETION			STATISTICS		
		Control mean	Drug mean	Change after drug	No. of control readings	No. of drug readings	Significant ratio of change
		sec.	sec.				
Billy.....	Strong excitatory (Bu)	4.6	3.8	−17	36	18	2.0
Sechs.....	Strong excitatory (Bu)	5.1	4.1	−20	35	18	2.5
Billy.....	Weak excitatory (M20)	6.1	5.3	−13	35	18	4.0

to an inhibitory stimulus. The latent period of the conditioned response to an excitatory stimulus increased with Vesal and was not altered with Conscription (Table IV).

The conditioned changes in respiratory and cardiac rates were

measured in three dogs, Billy, Sechs, and Conscription, and though only a few readings were made, the changes in the autonomic reflexes were in the same direction as those of the other conditioned reflexes, demonstrating, as will be explained below, a loss of differentiation.

TABLE IV

Effect of amphetamine sulfate on conditioned motor defense reflex and its latent period

DOG	CONDITIONED STIMULUS	MEASUREMENTS				STATISTICS		
		Measurement of	Control mean	Drug mean	Change after drug	No. of control readings	No. of drug readings	Significant ratio of change
			per cent	*per cent*	*per cent*			
Vesal.....	Excitatory	Per cent withdrawals of foot to stimulus (20 trials)	98	76	−22	21	10	2.8
Connie....	Excitatory	" "	97	95	−2	13	6	0.4
Connie....	Inhibitory	" "	0.8	13.3	+156	13	6	1.7
			sec.	*sec.*				
Vesal.....	Excitatory	Latent period of foot withdrawal	0.7	1.4	+100	20	10	4.1
Connie....	Excitatory	" "	1.66	1.68	+1	13	6	0.3

TABLE V

Effect of amphetamine sulfate upon unconditioned secretion to food

DOG	UNCONDITIONED STIMULUS	TOTAL UNCONDITIONED SECRETION			STATISTICS		
		Control mean	Drug mean	Change after drug	No. of control readings	No. of drug readings	Significant ratio of change
		units	*units*	*per cent*			
Billy.....	3 biscuits	828	760	−8	35	16	1.3
Sechs.....	3 biscuits	657	499	−24	28	18	2.7
Billy.....	½ biscuits	315	315	−17	34	8	1.1

The unconditioned secretory reflexes were measured in two dogs, Billy and Sechs. With both weak and strong unconditioned stimuli (2 gm. and 12 gm. food respectively) there was a definite decrease in unconditioned secretion after amphetamine (Table V), parallel to the loss of appetite.

TABLE VI

Effect of amphetamine sulfate upon unconditioned sexual reflexes

DOG	MEASUREMENT OF	MEASUREMENT			STATISTICS		
		Control mean	Drug mean	Change after drug	No. of control readings	No. of drug readings	Significant ratio of change
		sec.	*sec.*	*per cent*			
Billy	Duration of erection	167	110	−25	7	4	2.0
Sechs	Duration of erection	210	150	−28	4	3	3.7
Connie	Duration of erection	202	157	−24	6	6	2.5
Billy	Latent period of erection	44	49	+12	7	4	1.6
Sechs	Latent period of erection	24	25	+4	4	3	0.9
Connie	Latent period of erection	25	21	−6	6	6	0.7
Billy	Latent period of ejaculation	—	—	—	—	—	—
Sechs	Latent period of ejaculation	8	9	+12	4	3	0.5
Connie	Latent period of ejaculation	16	36	+125	6	4	2.1

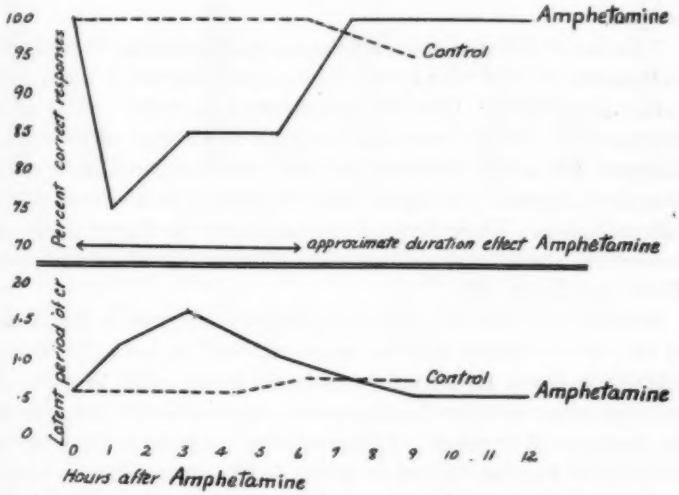

FIG. 2. DURATION OF EFFECT OF AMPHETAMINE SULFATE ON EXCITATORY CONDITIONED MOTOR DEFENSE REFLEX (VESAL)

The respiratory and cardiac rates became more labile after amphetamine, usually showing an increase.

The unconditioned sexual reflex, measured in three dogs, was definitely decreased in intensity soon after the drug, the duration of erection being shortened and the latent period of both erection and ejaculation slightly increased (Table VI).

For the next hour or longer after the drug the dogs became more active and often ran about restlessly.

The duration of the effect of amphetamine was determined on two dogs, Sechs and Vesal. The change in the conditioned secretory reflex (Sechs) and the conditioned motor defense reflex (Vesal) were used as measures of its effect, which began in each case in about half an hour, reached a maximum in one to two hours, and gradually disappeared until after six hours it could no longer be detected (Figure 2).

DISCUSSION

The chief effect of amphetamine upon the higher nervous activities of dogs was a moderate loss of differentiation, apparent in each dog, whether it was measured by the motor or autonomic conditioned reflexes.

This loss of differentiation after amphetamine sulfate is comparable to that after alcohol with a dose of 2.0 cc. per kilogram in dogs. However, amphetamine increased conditioned secretion while alcohol decreased it. On the other hand, caffeine in the dose of 16 mgm. per kilogram (to which amphetamine has been compared as a cerebral stimulant) increased the conditioned secretion to food without affecting differentiation. These comparisons are shown in Figure 3 (the data concerning alcohol and caffeine were obtained by Gantt (3) and by Wolff and Gantt (2)).

Amphetamine sulfate produced a moderate decrease in the intensity of the unconditioned reflexes measured; that is, both the secretory reflex to food and the sexual, possibly the motor reflex to pain. The question arises whether this decrease is responsible for any change in the conditioned secretion. This possibility is eliminated by comparing the ratio of the conditioned secretion to the unconditioned secretion under controlled conditions and after amphetamine. If this ratio remains constant, the change in conditioned secretion is due only to the effect on the unconditioned secretion; any change in this ratio denotes a direct effect upon the conditioned secretion. This ratio,

however, was increased (Table I), demonstrating that amphetamine increases conditioned secretion independently of any sympathomimetic or other action of the drug. Thus amphetamine has an excitatory effect upon the suprasegmental nervous system (the part chiefly responsible for conditioned reflex activity) but does not improve differentiation.

The site of action of amphetamine upon the unconditioned secretion was not determined. Since the drug is considered to have a sympathomimetic action it seems likely that the effect is upon the effector organ (salivary gland or smooth muscle) or the neuroeffector junction, but it

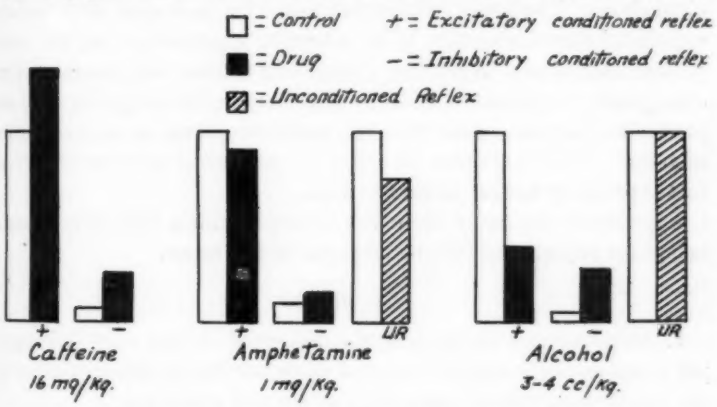

FIG. 3. COMPARATIVE EFFECTS OF CAFFEINE, AMPHETAMINE SULFATE AND ALCOHOL ON CONDITIONED AND UNCONDITIONED SECRETORY REFLEXES AND ON DIFFERENTIATION

may have an effect as well upon the peripheral or segmental nervous system. According to Cameron and Kasanin (13) amphetamine sulfate "appears to act through direct stimulation of smooth muscle and in other ways than through a specific sympathetic channel."

The increase in excitation of the cortex after amphetamine sulfate would tend to shorten the latent period of conditioned secretion, while the depressing effect upon unconditioned salivation would tend to lengthen the latent period. Since with both Billy and Sechs the latent period is shortened, the former effect appears to be more important with the conditioned secretory reflex. However, in the conditioned

motor reflex to pain the latent period was not altered as a rule, and was actually increased in one dog.

There are, then, three effects of amphetamine sulfate on the nervous system of dogs in the dose of 1.0 mg. per kilogram: loss in differentiation, excitation of the supra-segmental nervous system, and the possible inhibition of at least part of the segmental or peripheral nervous systems (secretory). Since theoretically each effect may be dominant under various conditions, this is a possible explanation for the variability in response to the drug.

These effects explain the results that have been obtained in rats, cited above. The loss of differentiation and the excitation of the supra-segmental nervous system is an adequate explanation for the poor performance of rats in running a maze and for the reappearance of an extinguished conditioned reflex. The increase in excitation also explains the increase in the rate of conditioning rats to an excitatory stimulus. It appears that the effect on the central nervous system of rats is probably similar to that in dogs.

Experiments to study the effect of amphetamine sulfate in human beings are reported in the second paper of this series.

CONCLUSIONS

1. Amphetamine sulfate administered orally to four dogs (1.0 mgm. per kilogram body weight) caused a moderate loss of differentiation in the conditioned reflexes (secretory, motor and autonomic).

2. Amphetamine sulfate increased the conditioned secretion relative to the unconditioned secretion to food, and thus was an excitatory stimulant of the supra-segmental nervous system. The latent period of conditioned secretory responses was shortened while that of conditioned motor defense reflexes was unaltered or lengthened.

3. The unconditioned secretion to food and the unconditioned sexual reflexes were decreased.

4. These effects on the nervous system began in about one half hour, reached a maximum in one to two hours, and could be detected up to six hours after oral administration of the drug.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Civilian Health in Wartime. By FRANCIS R. DIEUAIDE. 328 pp. $2.50. Harvard University Press, Cambridge, Mass., 1942.

Recognizing the importance of both physical and mental health of the nation as a factor in winning the war, the author presents to the general reader a broad but definite outline of the varied aspects of health in the United States. His point of view is that of positive health. Diseases and their treatment are not described. The theme of the book is not only the prevention of illness, but the betterment of the present day status of both physical and mental health.

The first chapters deal with nutrition which constitutes both an offensive and defensive weapon in modern warfare, and conclude with a full discussion of what is known regarding how to increase strength through better diets. The next five chapters discuss safety from infectious diseases, shelter and raiment, mother and child, the aging and the aged and occupation and recreation.

Then follows a discussion of the functions of doctors and nurses in the preservation of health, their part in the cultural pattern of this country and the problems of medical care that are before us both in normal times and during the war.

The last chapter deals with mental calm and vigor and is followed by an epilogue on morale during this war. Morale is described as mental health in respect to stresses and strains in a given period and set of circumstances. Its importance and its relation to psychological warfare is described with wisdom and with a broad understanding of human nature.

This book is written with unusual clearness and with the background of an experienced physician who has studied human beings intensely not only in this country but in the Orient. Much valuable material is brought together and presented so that the general public may understand some of the underlying principles that should be followed, not only as a factor in winning the war, but as essential factors in making us a stronger and happier nation in the difficult years that are sure to follow the war.

This book is a discussion of the problem of the upbuilding of health of the individual and thus of the nation, and as such it is timely, important and deserves to have a wide reading.

G. C. R.

Diseases of the Breast. By CHARLES F. GESCHICKTER. 829 pp., illus. $10.00, J. B. Lippincott Co., Phila., 1943.

This book fills a much-needed place in medical literature. It should be read by all physicians who see patients with diseases of the breast, whether internists,

surgeons, gynecologists, pathologists or radiologists. It is especially of interest to the general practitioner, for it is he who first sees the patients who suffer from diseases of the breast. With his extensive background in surgical pathology and laboratory research, the author is well qualified to write this very comprehensive book. To add value, there is a special section on treatment to which Murray M. Copeland surgeon and radio-therapist, has contributed heavily.

There are seven parts and 35 chapters. The first part traces the normal development and functional changes in the mammary gland with corresponding endocrine physiology in other organs. Part II has to do with "Breast in Pregnancy and Lactation," Parts III, IV and V with "Chronic Cystitic Mastitis or Mammary Dysplasia, Benign Mammary Tumors and Malignant Mammary Tumors," respectively. The subject matter in all of these parts is carefully arranged in an orderly fashion, each subject being completely and thoroughly handled, giving clinical features, diagnosis, pathology, prognosis and treatment.

Part VI on "Therapy" discusses all therapeutic agents including surgery, radiation therapy and hormone therapy, details of technique and doses in all forms of therapy being given.

Part VII, "The Experimental Production of Benign and Malignant Mammary Tumors," contains a vast amount of information discovered in the author's laboratory, as well as gleaned from the literature. In this part debatable issues are discussed thoroughly and fairly.

Throughout, valuable tables of statistics are given. The source of this material is from the literature as well as from the Surgical Pathological Laboratory of the Johns Hopkins Hospital.

The book is profusely and well illustrated.

The real value of this book is that one volume contains a mass of information pertaining to the breast, making possible ready reference to all phases of problems of the breast.

G. E. W.

Convulsive Seizures. By TRACY J. PUTNAM. 168 pages. Illustrated. $2.00. J. B. Lippincott Company, Philadelphia [etc.] 1943.

This is a very readable little book written for patients with seizures, their families and friends. Another chapter which these people are not supposed to read is addressed to lawyers and legislators. Dr. Putnam considers frankly the types and causes of seizures, modern refinements of diagnosis as well as the latest methods of treatment. He gives attention to matters of exercise, diet, work and the possibilities of psychiatric advice. Many may see objections to presenting to the patient in so clear a light the medical aspects of the convulsive problem. Patients familiar with the possibilities of brain tumor or status epilepticus may well have a fit.

O. R. L.

Behind the Sulfa Drugs. A Short History of Chemotherapy. By IAGO GALDSTON. 174 pp. $2.00. D. Appleton-Century Company, New York and London, 1943.

This book is more accurately described by the subtitle than by the title, for it summarizes the course of events in the entire field of chemotherapy. It is extraordinarily interesting.

One's attention is caught on the first page by a discussion of the precise meaning of the word "Chemotherapy" and of what distinguishes it from the older "Iatrochemistry". There follow brief but vivid sketches of Paracelsus and Boyle, of the pioneers in the coal industry and William Henry (Mauve) Perkin. Pasteur and Koch are introduced for the part they played in defining the objective. But the main body of the book is devoted to an analysis of the achievements of Paul Ehrlich. The account is necessarily abridged yet the image it presents of the many facets of this brilliant mind is three dimensional for all its compactness.

In the last two and one half chapters the story of the sulfonamides themselves is dealt with—somewhat sketchily, considering the title, and with what seems undue emphasis upon the Hopkins work. However, let us not quibble over that!

There are two statements to which one does take exception. One is a reference to poliomyelitis, influenza and the common cold as bacterial diseases. It is probable that the resistance of these infections to sulfonamide therapy—the problem which the author is discussing—is the result of their being of virus and not of bacterial aetiology. Then, not once but twice, sulfanilamide is described as a dye. This error is a grievous one to the present reviewer who has a pet theory that the reason sulfanilamide lay unrecognised for twenty-five years was precisely because it was not a dye. Attention was so riveted upon specificity and the selective action of dyes that a colourless substance just did not stand a chance. It is queer that Dr. Galdston made this mistake for he appears to have had the same idea in the back of his mind. With real astuteness he lays the blame for the "doldrum years" upon Ehrlich's dictum: *Corpora non agunt nisi fixata.*

These lapses, while annoying to the specialist will do the general public no harm, nor do they detract from the interest which the book as a whole will have for the scientist who wants to know how chemotherapy came about.

E. A. B.

Diagnosis of Uterine Cancer by the Vaginal Smear. By GEORGE N. PAPANICOLAOU and HERBERT F. TRAUT. 47 pp. 11 pl., $5.00. The Commonwealth Fund, New York, 1943.

The first chapter of this monograph deals with the technique of obtaining and staining vaginal smears. The second chapter presents a classification of the cell types found in the vaginal fluid. The third chapter is concerned with the cellular contents of the vaginal fluid at different periods of the normal sex cycle. The fourth chapter discusses the cellular contents of the vaginal fluid during modified physiological and pathological conditions.

The remainder of the volume is concerned with the vaginal smear in relation to the diagnosis of cancer of the genital tract and, particularly, cancer of the cervix and endometrium. The report is based on "probably between seven and ten thousand vaginal smears" from 3,014 adult women. In this group 179 women were found to have primary cancer of the uterus and there were 14 more in whom there was cancer of the ovary, bladder, urethra or vulva. The authors conclude that the method has its greatest value in the diagnosis of cancer of the cervix. If post-radiation cases are excluded from the series of cervical cancers there was an incidence of false negatives of only 1.6 per cent out of 127 cases of proved lesions. Among the cases diagnosed as cervical cancer were a few which could not have been detected clinically or by the use of biopsy since there was no clue as to where a biopsy should be taken. The diagnosis of adenoma malignum of the endometrium and also of the cervical canal was particularly difficult. The diagnosis of adenocarcinoma of the endometrium presented greater difficulties than cervical cancer. Excluding the post-radiation cases there was a failure to diagnose adenocarcinoma of the endometrium 7 times out of a total of 53 cases in which it was diagnosed by curettage. This was offset, however, by 9 instances in which the presence of the tumor was revealed by vaginal smear when the patients gave no clinical symptoms suggesting cancer. On two occasions vaginal smear revealed adenocarcinoma correctly when repeated curettage failed to do so because of the inaccessible location of the lesions.

It is the opinion of the reviewer that the authors have proven their point that malignancy of the genital tract can be detected by vaginal smear in a high percentage of cases. It should be stressed, however, that this can only be done when expert cytologists examine properly prepared specimens. It should not be used as a substitute for cervical or endometrial biopsy but if used as an adjunct a rare case of carcinoma may be picked up which otherwise might be missed. Certainly, negative cytological findings should not deter one from doing a curettage or cervical biopsy when clinical symptoms suggest the possibility of malignancy.

R. W. TeL.

Fractures of the Jaws and Other Facial Bones. By GLENN MAJOR. 446 pp. Illus. $7.50. The C. V. Mosby Company, St. Louis, 1943.

As a statement generally true and particularly true in these times of dislocated practice, it is safe to say that fractures of the jaws and other facial bones are less satisfactorily treated than are other fractures. There is definite need for a book which will place in the hands of the general practitioner the basic information which will enable him to deal with these fractures more effectively either from the point of view of first aid or, in the absence of a more skilled consultant, in the definitive treatment and after care. Doctor Major's book competently satisfies this need and in addition will be found very useful by surgeons who have had experience with this type of fracture.

The arrangement of the book is logical and helpful. It progresses in an orderly

manner through the general discussion of these fractures and includes diagnosis, the mechanics of displacement, the general principles of treatment and the general types of fixation. The special fractures are then described in more detail. The illustrations which were drawn by the author are clear.

Other than suffering from the excessive use of "and/or" the literary quality of the book is satisfactory and the author's ideas are clearly expressed. The index seems complete and the book is an excellent reference for surgeons who would improve their ability to treat these fractures which are so deforming and disabling when badly treated.

E. M. H.

BOOKS RECEIVED FOR REVIEW

Manual of Industrial Hygiene and Medical Service in War Industries. Issued under the Auspices of the Committee on Industrial Medicine of the Division of Medical Sciences of the National Research Council. Prepared by the Division of Industrial Hygiene, National Institute of Health, United States Public Health Service. WILLIAM M. GAFAFER, Editor. 508 pp. Illus. $3.00. W. B. Saunders Company, Philadelphia and London, 1943.

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Textbook of Anatomy and Physiology for Nurses. By CARL C. FRANCIS, G. CLINTON KNOWLTON, and W. W. TUTTLE. 586 pp. Illus. $3.50. The C. V. Mosby Company, St. Louis, 1943.

Methods for Diagnostic Bacteriology. By ISABELLE G. SCHAUB and M. KATHLEEN FOLEY. 2nd ed. 430 pp. $3.50. The C. V. Mosby Company, St. Louis, 1943.

History of Nursing. By DEBORAH MACLURG JENSEN. 310 pp. Illus. $2.75. The C. V. Mosby Company, St. Louis, 1943.

Primer of Allergy. By WARREN T. VAUGHAN. 2nd ed. 176 pp. Illus. The C. V. Mosby Company, St. Louis, 1943.

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Principles and Techniques of Nursing Procedures. By SISTER MARY AGNITA CLAIRE DAY. 574 pp. Illus. $3.50. The C. V. Mosby Company, St. Louis, 1943.

Atlas of Obstetric Technic. By PAUL TITUS. 180 pp. Illus. $7.00. The C. V. Mosby Company, St. Louis, 1943.

Whooping Cough. By JOSEPH H. LAPIN. 238 pp. $4.50. Charles C. Thomas, Springfield, Ill., 1943.